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## EDITORIAL

### PREVENTIVE MEDICINE\*

**I**N a very interesting address to the Undergraduate Medical Society, by the Dean of the Medical Faculty of McGill University, a strong plea was made for the wider application of the principles and a more thorough investigation in the field of Preventive Medicine. Associated with the marvellous progress which has been made in the last quarter of a century, the development of the scientific spirit and the growth of the new motive of humanitarianism, were held as important factors. A number of statistical facts were presented in most convincing form to show what has already been accomplished in the realm of Preventive Medicine.

To demonstrate the effect of vaccination as a preventive measure against smallpox, an analysis of deaths from this disease in the City of Detroit in 1914 was made. There were 163 deaths in that year, and in this number 88.5% had never been vaccinated; 11.5% had not been vaccinated within 10 years; and there were no deaths reported where vaccination within 10 years had been done. In the field of Diphtheria before and after the discovery of antitoxin remarkable strides have been made. In a 5 year period (1891-95) before use of antitoxin the Diphtheria mortality rate in Philadelphia averaged 124 per 100,000. In contrast to this a 5 year period (1906-10) after antitoxin was in fairly general use, showed a drop in the mortality rate to 33 per 100,000. To show the value of Typhoid vaccination interesting facts were given. During the South African War the case mortality was 13.8%; and during the Great War, 1914-18, where ten times as many allied soldiers were involved, the case mortality was only 5.9% on all fronts, and only 3.3% on the French front. In the case of Malaria statistics kept in fifty-one southern and south-western cities on this continent showed a fall in the death rate from Malaria from 14.1 per 100,000 to 3.5 per 100,000 during 1911-1920. In Tuberculosis remarkable results in the field of preventive medicine in the City of Toronto have been obtained. In a period from 1913-1921 the death rate per 100,000 has fallen from 105 to 66, nearly one half. In England the mortality rate per one million population in 1847 amounted to 3181, whereas in 1921 it amounted to

\*Reviewed from Dr. Martin's address in the January issue of the Canadian Medical Association Journal.

853. With the modern changes in sanitation methods the death rate in infants from Diarrhoea and Enteritis has shown a striking fall also.

In contrast to the above facts, statistics were presented illustrating the conditions where diseases exist for which no adequate public measures are adopted—heart disease and cancer—and it was shown that the mortality rates have remained practically unchanged in the last 10-25 years.

Another extremely interesting and important point was alluded to in relation to state expenditure for Public Health work. The cities of Montreal and Toronto were contrasted in this respect, and the following facts were presented:

|                                                               | Toronto    | Montreal   |
|---------------------------------------------------------------|------------|------------|
| Expenditure on Public Health by City                          | \$835,000  | \$272,000  |
| Health Department                                             | or \$1.60  | or \$0.42  |
|                                                               | per capita | per capita |
| General Death Rate per 1000.....                              | 11.4       | 15.6       |
| Tuberculous Death Rate per 1000.....                          | 65.0       | 152.5      |
| Typhoid Fever—total deaths.....                               | 13.        | 47.        |
| Infant Deaths, per 1000 live births.....                      | 71.0       | 148.9      |
| Diarrhoea and Enteritis, total deaths under<br>two years..... | 87.        | 1249.      |

There are 4.2 less persons die per 1000 of population in Toronto.

If Montreal's population is 600,000 there would be a saving of 2,520 lives yearly, if the rate were lowered to the Toronto level.

The inferences which may be drawn from these facts are obvious. In this regard Dr. Martin stated that the importance of adequate expenditure by the state is scarcely realized, though to the expert it is obvious that where public authorities are willing to spend money far-reaching beneficent results may ensue.

In considering the relation of medicine to society he pointed out that increasing knowledge brings added responsibility to the practitioner of medicine. To the conscientious practitioner prevention and practice are inseparable. At present there is, on the part of society at large, an obvious trend to promote community welfare. This is evidenced by the fact that welfare clinics have been organized in practically every city on the continent, to promote health and to prevent disease. Especially important is the work being accomplished along the lines of child health, prenatal and postnatal work, dental work, mental hygiene, industrial health, etc. State laws are being enacted with a view to prevention of disease, and also to combat the manufacture of impure foods and to control the use of harmful drugs. Dr. Martin further pointed out that it is quite reasonable to expect that considerable strides will be made along these lines, and in all probability the future practitioner of medicine will be a counsellor of health, endeavouring not so much to cure disease as to prevent its occurrence. He stressed the importance of knowing the normal as an important factor in the application of the principles of hygiene in the community at large.

In order that Preventive Medicine may at present be established on a more efficient working basis he claimed that the intelligent co-operation of the general practitioner with the officers of health, and the district in

general, is essential. The necessity of infusing the preventive idea throughout medical education was emphasized, so that the outgoing graduate may have uppermost in his mind the desirability of prevention rather than the cure of disease.

In closing he stated that preventive medicine is no longer a pious hope, but a very practical aim, and he who can counsel wisely for the maintenance of the *mens sana in corpore sano* is verily one of the greatest benefactors to society at large—because, after all, the building up of normal manhood and womanhood is the greatest asset of which any country can boast.

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### BACTERIOPHAGE

THIS is a subject of particular interest to our readers in that it is so closely associated with the name of one of our countrymen, d'Hérelle, to whom was recently awarded the Leeuwenhoek Medal. This award is in memory of that "Pioneer Microscopist" who was the subject of a recent biography in this journal.

d'Hérelle's first report in 1917 followed upon an unobserved paper by F. W. Twort published two years previously, and the substance of their work is now commonly known as the "Twort-d'Hérelle phenomenon." This, in brief, consists in the property of an invisible and apparently living agent known as Bacteriophage or simply phage to destroy bacterial growth. The phage itself lives only in the presence of new bacterial growth from which it can be separated by filtration. The resulting "disease" of the bacteria can be passed from culture to culture *ad infinitum*, the phage apparently increasing continuously in quantity.

Discovered by d'Hérelle in the intestinal tract of man, phage was also found in that of the higher animals, as well as in pathological tissues, exudates, bacterial cultures, soil, water, etc.

If present, it is contained in the sterile filtrate of a broth culture made from a small portion of the bacterial containing material. On the addition of some of this filtrate to young broth or agar cultures of various bacteria its presence is indicated by the inhibition of the growth, the clearing of the broth cultures and the abnormal watery, moth-eaten forms of the colonies on agar.

Different bacterial species manifest varying degrees of susceptibility to the action of phage. Some species are extremely susceptible, while others apparently are absolutely resistant. The virulence of a sample of phage for a given strain of bacteria is measured by determining the smallest amount that will inhibit or otherwise affect the growth of the culture. In certain cases bacterial cultures would not develop in broth containing one-trillionth part of the filtrate from a culture on which the phage had been allowed to act.

Both the range and degree of virulence may be modified by artificial means, such as "passage" in vitro with different kinds of bacteria. For example, a phage extremely virulent for a certain strain of *B. coli* also manifested a slight degree of action on strains of *B. dysenteriae*,

*B. typhosus* and *B. paratyphosus*  $\alpha$  and  $\beta$ . After propagation in cultures of the *B. dysenteriae* for eighteen months it no longer affected cultures of the colon bacillus, but was exceedingly virulent for the dysentery organism. Its power to affect the other bacteria had not been appreciably altered.

As a rule, phage is more resistant to heat than are the bacteria in which it grows, thus making it possible to separate them by means of heat. The same applies to a number of chemical antiseptics.

A not very potent antiserum is developed in rabbits given a series of injections of fluids containing phage. The immune serum is tested by mixing it with an active phage, allowing the mixture to stand at 37° C. for thirty minutes and letting a drop or two of it flow across the surface of agar which has been innoculated with sensitive bacteria. If the phage has been neutralized the entire surface of the agar will be covered with bacterial growth, while if the phage is still active the path of the drop will remain free from bacterial growth.

d'Hérelle formulated a new and interesting theory of immunity, in which are involved the Bacteriophage and cellular and antitoxin immunity. Typhoid bacilli entering the organism are killed off by the phage present if the subject is immune. If a virulent phage is not present disease results, and recovery is due to the developing of virulence by the phage with consequent destruction of the invading organisms. The phage may be able to oppose the bacilli sufficiently to prevent disease but not be able to destroy them, and a typhoid carrier results. If the phage is absent, or present and unable to interfere with the growth of the bacilli, a fatal infection develops. d'Hérelle next supplied a virulent strain of phage in several epidemics amongst fowl and other animals in which it was absent and met with universal success. The results reported show a very striking and rapid development of immunity. Results with dysentery cases were just as satisfactory, and d'Hérelle reports that bacteriophage leaves nothing to be desired in the prevention and cure of infectious diseases and seems "too good to be true." Unfortunately, subsequent workers have failed to observe any benefit from such treatment and find judgment on phage as a preventive, and therapeutic agent, must await further observation.

d'Hérelle believes that the bacteriophagous phenomenon is the manifestation of the activity of an invisible organism—the ultra-microbe—a parasite of living bacteria, and ordinarily it lives at the expense of saprophytic intestinal bacteria but possesses a potential virulence for many pathogenic bacteria. He bases this living virus hypothesis chiefly upon the following facts: (1) The bacteriophagous element grows. (2) It exists in particulate form as evidenced by the growth of the distinct "colonies of phage." (3) It has the property of adaptation as shown in the acquisition of virulence for bacteria and increased resistance to chemical agents. (4) It penetrates bacteria and multiplying within them causes fragmentation. (5) The secreted ferment may be separated from the ultra-microbe itself. (6) A specific antibody has been discovered and (7) his experiments indicate a decisive rôle in resistancy to and recovery from disease.

The ultra-microbe theory has been vigorously assailed. Kabéshima feels that a living agent could not survive the temperatures and chemicals

to which phage is resistant and favours a catalytic agent as the true cause.

Bordet and Ciuca advance the hypothesis that the whole phenomenon may be looked upon as the manifestation of a nutritional disease of bacteria, which is not only inheritable but contagious as well. The disease first arises as the result of the action of defensive agents, particularly leucocytic exudates of an infected host.

Bail thinks the agent arises from the bacteria themselves under certain conditions and calls it "splitter" (something of the nature of a chromosome?) He thinks that "splitter" may be pathogenic and that typhus fever is probably caused by the "splitter" from the Weil-Felix *Proteus bacillus*.

Otto, Munter and Winkler believe that as the result of some particular stimulus—animal tissues or fluids, or bacterial products, bacterial variants, having exaggerated autolytic properties, arise with an increased formation of the stimulating substance, until the concentration reaches the advanced stage seen in the Twort-d'Hérelle phenomenon.

All these theories require the assumption of phenomena which are as yet unproved and for which we have no exact analogy. Few, if any, of them are more plausible or less fanciful than the ultra-microbe hypothesis. Final decision as to the nature of bacteriophage must therefore await the production of future evidence.

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#### PROGRESS OF THE JOURNAL

THE JOURNAL is continuing to meet with very gratifying success. Contributions of high standard have been freely proffered by both staff and students. To these we tender our sincere thanks for rendering our task the easier. To those who have not contributed we urge the expediency of doing likewise. The JOURNAL is apparently attracting considerable notice in other centres to judge from the requests we receive for the insertion of news items, many of which, unfortunately, can prove of very little interest to our readers. It has already reached our attention that no less than two articles from our November issue have been reprinted in other medical publications. Encouraged by a greatly increased circulation, the JOURNAL has become considerably enlarged. This and the preceding number are, with the single exception of the concluding issue of Volume I, larger than any previously published number, and are each some ten pages in excess of the average length of last year's issues. Unfortunately, our sales amongst the student body, although higher than ever before, fall far short of a satisfactory level. Despite the fact that many of the articles are of no immediate interest to the junior years the fault is no more theirs than throughout the remainder of the faculty. Unlike such publications as *The Varsity*, it has no compulsory 100 per cent. circulation of the student body. The JOURNAL is yours. We feel that it should be voluntarily given the support of each of the 800 students in our faculty. We regret to state that even with a quite large outside circulation we sell considerably fewer copies than this. The last issue lost money, but we are publishing this in the confidence that increased support will prevent our having to return to a smaller list of contents.

## 1876-1926—THEN AND NOW

ALEXANDER MCPHEDRAN, M.D., LL.D.  
*Professor Emeritus of Medicine, University of Toronto*

The contrast between the four six months sessions in 1876 and that of 1926 with its six eight months sessions is as great as the advance in the development of medical science and practice during the fifty year period.

In the former period there were only two laboratory courses, anatomy and practical chemistry. The latter was given by the late Professor Croft, who depended on the lucidity of his lectures and demonstrations to secure attendance of students; he called no roll as the other professors did. His faith was not misplaced. All the other courses, including clinics, were given as theatre lectures, some good and others not attractive, so that books, not all good, were depended on for the necessary information.

The lectures were given in an old building that stood where the Biology Building now stands. The lecture room was arranged in theatre manner and furnished with pine benches, very inviting for cutting with pocket knives; the penknife artists made the best of the opportunity. In my year there were not more than twenty students; although so few, the decorum was not always ideal. If one who was thought to be "cheeky" took a front seat, he might be picked up while waiting for the teacher and passed up on a relay of hands and dumped on the top bench. On one occasion the lecturer took a hand. The lecturer on anatomy, a very able and irascible man, thought a rude remark was made by a man on the top bench; he went up and took him by the collar and hurled him down to the bottom and then ran him out of the room. It was the custom to stamp and often shout when a lecturer entered. The habit persisted even after the School became the Faculty of Medicine in 1887 and continued into the present century. By that time the number of students filled the large room in the northwest part of the old medical building. Such demonstrations were very unseemly, especially if a distinguished visitor was present. Requesting that it be stopped had no effect, so I went "on strike" for two weeks until they agreed to the request, for my lectures at least. The effect was salutary and gradually spread to other lecturers.

Our examinations were all written; we had to write on pass and honour papers, the pass in the forenoon and honour in the afternoon, so that honour men had to write two papers a day, for two weeks. The final year examinations included every subject in all the courses from the first year up, taxing work on the memory but little on the judgment; the object being to make certain they were proficient in all the subjects of the course, a laudable aim.

I would not have you infer that our teachers, at least several of them, were not able men. They did their work after the manner in which it was done in Europe and America. The late H. H. Wright, Professor of Medicine, was remarkably well read and had a phenomenal

memory. He could always tell me where to find a desired reference, not only the book but often the page. Dr. W. J. Aikins, Professor of Surgery, introduced antiseptic surgery in its earliest days and practised it, although the antagonism to it was very great, as it was in Britain and the United States. Dr. Uzziel Ogden, Professor of Obstetrics and Gynaecology, was the best therapist that I had met. All three were most kindly to beginners. They were men of high ideals, comparing at least favourably with those of the present day.

In the earlier days there were no specialists except in Ophthalmology; they included also nose and throat diseases in their work. All the others were general practitioners, each member of the hospital staff taking his quota of medical and surgical cases. A few years later a division similar to present conditions was made.

There were no ward clinics, but some of us, greatly feeling the need of ward instruction, arranged with a junior lecturer for private bedside clinics with patients we had already examined and taken histories. We also had a weekly conference in the evening on our work. It will be seen that the ward clinic, one of the first in Canada, was initiated by the undergraduates long before it came into being in the U.S., although its full development was slow and it did not become general for some years. In the late nineties there was a meeting in the New York Academy of Medicine to hear an address by the late Sir William Osler on clinical teaching. He advocated the ward bedside method as you all know it. It was a very large meeting, including men from all the medical schools of New York and neighbouring cities; but not one present, except myself, supported the views of the lecturer. Next day a professor invited me to a ward clinic. He assembled his class in the centre of the ward, and then pointed out some patients, only one of which showed any signs recognizable at the distance, telling them their symptoms and signs. On being asked why students should not be admitted to the ward to take histories and make physical examinations, he said the patients would not tolerate it, and that the benefactors of the hospital objected to what they regarded as an indignity to the patients. It was a pleasure to assure him that, with us, patients in the rare exceptions welcomed the student and regarded his examination as important; and that donors for the hospital's upkeep recognized the great value of the practice, not only to the students and hospital patients so long as with due decorum, but especially to patients in outlying districts by the improved training of physicians on whom they had to depend for care and treatment. You can contrast this with your privileges in the ward, privileges that have fully existed since the organization of the Faculty of Medicine, 1887.

Laboratories began to be formed then; you know to what extent they have now developed.

The principles and methods of treatment have advanced in like manner. Then the aim was to give such drugs as would relieve the symptoms—drugs often nauseous and repulsive. For example, for diarrhoea a mixture such as this: Tinctures of rhubarb, opium and rhatamy, chalk, syrup and water, a mixture so objectionable that it can be realized only by seeing and tasting it. It was not realized that it was only necessary to give a mild purgative as castor oil, the best, to

expel the irritating material in the bowel, rest in bed and water plentifully. Is it unreasonable that homeopathy flourished? Typhoid fever prevailed throughout the year, especially in autumn, as it was not realized that impure food and water and bad drainage were the causes. Sanitation had not been discovered. Every autumn one-third or even one-half of the medical wards were filled with cases, and the death rate was appalling. About 1890, in October, a ward of twenty beds, twenty-eight patients were admitted, all robust men from city and country—eight, nearly one-third, were taken out on stretchers. It was very depressing. It was even worse in my student days. At that time malaria was widely prevalent, as the anopheles was common, breeding in marshes and along slow streams as the Don and Humber. Oakville had an unenviable reputation.

In all the branches of medicine phenomenal advance has been made, notably in surgery, and all its specialties due to Lister's great discoveries. Antiseptic treatment was introduced into Toronto about 1879. There was much antagonism to it here as in nearly all other countries, owing to a lamentable lack of vision of surgeons. So great was the antagonism that on one occasion at least the dressings were opened and pus put into the wound, a dastardly act, almost beyond belief.

At that time some surgeons operated in their frock coats. They turned up their coat sleeves, washed their hands in a basin of water which was usually left grossly filthy, not even using the open tap to carry away the dirt, altogether an amazing matter even to thoughtful students in those days, and washing the part to be operated on in an equally uncleanly manner. No special care was taken to prevent contamination of the wound, so that suppuration as a rule followed and gangrene not rarely.

Apart from smallpox, syphilis and malaria, there were no known means for prevention or curing diseases. Contrasting that with the vast number of ailments that can be controlled and cured now, the great advances made can be realized. Typhus, tetanus, gangrene and many others have been prevented or relieved. The outlook in tuberculosis is greatly improved, many cases being restored to health and efficiency, and so it is with the epoch-making discovery of insulin.

Sanitation was very elementary. It was some years later that Health Officers were appointed in the larger cities. Preventive medicine, including means for promoting public health, was not thought of. No aspect of medicine has made greater progress in development, and done more, not only for the physical well-being of humanity, but also of the animal world. To note only a few of its achievements, it has impressed the importance of fresh, clean air, sunshine, cleanliness in the widest sense, rational living and the care of children. It has shown the way to the prevention of many diseases, such as typhoid, typhus, yellow and other infection. It has added to the longevity in all civilized countries.

Contrast the then conditions with those of to-day and you will realize the phenomenal progress made and make you glad that your lot is cast in better times. However, there is still a long way to go in research and in development of medical science and practice. The opportunities are many and attractive. It is for you to show appreciation of and do credit to the training and facilities that have fallen to your lot.

**THE ETIOLOGY OF PERNICIOUS ANAEMIA**

FRANK A. TURNBULL, B.A., '28

There are many and varied definitions of this disease, but the original description of Addison in 1855 is still the one most generally accepted—"a general anaemia occurring without any discoverable cause whatever; cases in which there had been no previous loss of blood, no existing diarrhoea, no chlorosis, no purpura, no renal, splenic, myasmatic, glandular, strumous or malignant disease."

The progressive pernicious anaemia of Biermer (1871) and that of most subsequent authors—W. Hunter and C. Alport being the outstanding exceptions—embrace much more than a single pathological entity, but their differences are less clinical than pathological.

Hunter (1), who has been persistently misquoted in the literature, terms the idiopathic anaemia of Addison "glossitic anaemia" because of the presence of history of "sore tongue" in patients suffering from the disease. He distinguishes glossitic anaemia from all other anaemias by two outstanding etiological characteristics:

1. Its most peculiar sex and age incidence—71% of the cases in men, 85% over the age of 40.
2. The marked seasonal character of its onset and of its periodic relapses—namely, July to September for its onset, and approximately the same months for its relapses. This places the disease within the category of specific infective diseases in such a striking way that this character of it can be no longer in doubt. "This character is notably absent in the anaemic condition, which, when severe, most closely resembles it, and is most frequently mistaken for it—the anaemia which I have differentiated and term 'septic anaemia'."

Oral sepsis, according to Hunter, is an intense complication, but not the cause of glossitic anaemia. The former lesions are connected not with the tongue but with the teeth. This oral sepsis itself can, and often does, cause a form of anaemia quite different from the haemolytic anaemia of the sore tongue disease in being non-haemolytic, and in owing its character to defective haemogenesis—just as much as the haemolytic anaemia owes its character to excessive blood destruction and subsequent exhaustion of the haemogenetic tissues.

In pernicious anaemia excessive haemolysis is taking place. The fact that poisoning by such chemicals as toluylendiamine, nitrobenzole, etc., may produce blood states practically indistinguishable from pernicious anaemia indicates that haemolytic poisons are the cause.

Some authors ascribe the disease to a gastro-intestinal disturbance, leading to injury of the mucosa, and the absorption of haemolytic toxins of putrefactive origin or undigested proteins, which in the blood stream become transformed into haemolytic poisons. It is difficult to say with certainty whether the oral and intestinal sepsis cause the anaemia or whether they arise because of it and the lessened resistance to infection which its presence may entail.

Hurst (2) says that pernicious anaemia is caused by some infection in the alimentary canal, and states that this infection cannot take place

unless free HCl is completely absent from the gastric contents. The achlorhydria allows the bacteria which produce haemolytic toxin, and which probably have their primary focus in the mouth, to pass through the intestines without being destroyed by the HCl which ought to be present. He points out that:

1. There is generally a more or less long history of digestive disturbances preceding the first symptom of anaemia.
2. In 164 out of 166 test-meals, carried out under his direction at Guy's Hospital and the London Hospital, on cases of pernicious anaemia, achlorhydria was complete. It is a more constant symptom than any other, even than the haematological signs, such as high colour index.
3. The achlorhydria is not specific, but whatever its origin it predisposes to the development of pernicious anaemia. Thus in many cases the history points to its being congenital or "physiological." Bennet and Dodds (3) disagree with Hurst and state that the hyposecretion seen in pernicious anaemia is entirely secondary to the anaemia itself.

They state that:

1. The elements which constitute the secretions of the glands of the alimentary canal are derived from the blood stream; a radical alteration in the constitution of the blood may produce a radical alteration in the alimentary secretions.
2. Patients suffering from pernicious anaemia almost invariably show complete achlorhydria; many of them show, in addition, a disturbance of digestion suggestive of pancreatic insufficiency.
3. The curve of alveolar CO<sub>2</sub> tension in patients suffering from pernicious anaemia is markedly different from that given by a healthy man with achylia gastrica, the difference being of a type suggesting that the pancreas as well as the stomach is involved.
4. Patients with anaemias other than of the pernicious type show, to a lesser degree, similar abnormalities in their curves of alveolar CO<sub>2</sub> tension.

There are many conditions which from their association with pernicious anaemia have been regarded as more or less causal factors in its etiology. Whether they are truly causal or simply coincidental, or what their relation to the disease is, has not been definitely established. A certain number of cases seem to originate in relation to pregnancy (4)—some may be preceded by loss of blood, severe vomiting, and diarrhoea; others arise without definite cause, and progress fatally. These latter are apparently related to the physiologic anaemia in the early months of pregnancy. A syncytial haemolysis in the ectodermal cells of the chorion is the source of the haemolysis in the early pregnancy (Hofbauer). In the second half of pregnancy an antihaemolysin is formed in the maternal blood (Hofbauer). If the latter function fails for any reason there continues an active haemolysis and a progressive anaemia during pregnancy. The toxemias of pregnancy may be related to, or at least associated with, the anaemia.

Gastric and other carcinoma may be looked upon as definitely related to the anaemia, if by metastases to the bone-marrow the effect is to produce a megaloblastic anaemia.

One particular form of anaemia so resembles the pernicious variety in its symptoms and blood picture that it may be regarded as an example of the disease, the cause of which we know, and which can be cured by proper treatment. This is *Bothriocephalus* anaemia due to absorption of the products of decomposition of the parasite, which results not only in haemolysis but by its action on the bone-marrow in megaloblastic blood formation. The onset of the symptoms is coincident with the death of the worm (5). Tallquist succeeded in extracting from *B. latus* a lipid-like body which had a strong haemolytic action. Here we can speak of a variety of pernicious anaemia, the etiology of which is known.

The tendency to treat pernicious anaemia by splenectomy associates it with the theory of hypersplenism (7). Eppinger and King consider that the amount of haemolysis in a given case is in definite relation to the amount of unsaturated fatty acids and the amount of urobilin in the faeces. They found that the unsaturated acids in pernicious anaemia rise from a normal (iodine number) of 80-90 to 188-273. They found that removal of the spleen in the dog caused a great drop in the iodine number and was associated with an increased resistance of the red cells and lessened tendency to haemolysis.

Alport (6) has recently suggested an hypothesis, which, though not backed up by sufficient experimentation, gives one a stimulating viewpoint for the etiology of the disease. He states that the primary factor is the phagocytic action of the liver and kidneys, and that the bone-marrow change is secondary, the latter being due to an increased and urgent demand for red cells to replace those destroyed. The cause of the increased destruction is not an unknown toxin, but an unknown substance normally present in the blood, the diminution or absence of which renders the blood increasingly liable to phagocytosis by the epithelial cells of the liver, etc. To prove this he prepared an extract from blood by the alcohol-fractional precipitation method, which is freely soluble in water, non-toxic, and apparently has some effect in increasing blood formation. This extract—termed “sanguinin”—apparently either temporarily stimulates blood formation or temporarily inhibits blood destruction.

This paper, which is essentially a review of the literature on the subject, can offer no conclusions beyond pointing out that the majority of observers ascribe pernicious anaemia to various causes, which produce a protracted slight haemolysis that continues until the haematogenous organs give out, their exhaustion being perhaps hastened by the influence of the toxic substance in the blood; haematogenesis then becomes insufficient to replace the lost corpuscles, and the picture of pernicious anaemia is established.

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**DECOMPOSITION IN INFANTS**

By L. NELLES SILVERTHORNE, '26

*Definition*

This condition is a chronic state of malnutrition seen in infants, characterized by the inability to assimilate food, by loss in weight, by emaciation and dehydration, by a subnormal temperature and lastly by a lowered resistance to infection. It is also known as atrophy and marasmus.

*Etiology*

The main etiological factor seems to be improper nourishment, which results from changing the feeding from one kind to another over a comparatively short interval of time, *i.e.*, a period of a few weeks to two or three months. L. E. Holt claims decomposition is rarely seen in private practice or rural districts, but it is of frequent occurrence in institutions and larger centres. In the latter, fully half the deaths under one year of age are directly or indirectly due to decomposition, although the cause of death is often attributed to some other disease: the determining factor is frequently a previous marantic condition. Parenteral infections and nutritional disorders play an important role in predisposing the child to decomposition. It occurs in breast-fed infants, being associated with improper nourishment and digestive upsets, and leading to disuse and subsequent atrophy of the gastro-intestinal system. Other factors are overcrowding, uncleanness, lack of sunlight and fresh air. This condition usually develops before the third month, and the earlier in life it occurs the poorer is the prognosis. Frequently a history of dyspepsia or intoxication is obtained.

*Pathology*

In Abt's System of Paediatrics different workers explain the existence of atrophy. Finkelstein observes that undernourishment is not the cause of atrophy, nor does he believe that atrophy follows dyspeptic conditions, which are the result of internal etiological factors. He thinks the condition is due to abnormal chemical processes in the intestine, and that excessive loss of body fluids only is capable of producing atrophy. These infants are both hungry and thirsty, and show an inability to combine water with the tissues in spite of the fact that water is administered in abundance. On the other hand, Czerny believes that atrophy is due to a low assimilative capacity for fat with an excess of fatty acids formed in the intestinal tract. These fatty acids combine with the alkalies of the body tissues and undergo neutralization. In this process of demineralization the potassium and sodium salts are lost in the soap stools. The loss of weight in these infants is produced by any change which interferes with imbibition of the cells or tissues, whether this be underfeeding or insufficient supply of water and salts. The same authors suggest that the constitutional state of the infant is significant, that is to say, infants differ in their ability to retain water. Some babies readily give up water, whereas others, in which there is not this water instability, retain it very well, the former

being more prone to develop decomposition. Post mortem findings throw little, if any, light on the cause of the condition. Congestion in the different organs may be found, especially in the liver; but, apart from this, autopsy findings are negative.

### *Clinical Signs and Symptoms*

Most authors describe the same characteristic symptoms in a case of decomposition. On account of the chronic onset of this disease it is not recognized in the early stages, and the only symptoms observed are after the condition has progressed for some time. Briefly, the history is as follows: At birth the child was a normal healthy infant, plump, well-nourished and continued to thrive for a month or so, while on the breast. Then circumstances necessitated weaning; from then on the infant ceased to thrive, lost weight and finally, after several forms of infant foods have been tried, the child was brought into the hospital in a wasted condition resembling a skeleton. The general appearance is characteristic; the face is that of an old man, the skin is wrinkled, has lost its tissue turgor and hangs in folds upon the extremities. Subcutaneous fat is absent, the abdomen is prominent, the legs are like drumsticks, and the fontanelle sunken. The whole expression is one of eagerness due to starvation. Anaemia is often present, the temperature is subnormal, and there is a diminished resistance to infection. General oedema is also seen in some cases, and is usually first noticed when there is an unexpected gain in weight amounting to several ounces a day. Diarrhoea is common, the stools containing undigested food and mucus, but occasionally constipation may be seen. Vomiting is a common symptom and is readily excited. There is often a peculiar rigidity to the musculature, especially marked in the legs.

### *Complications*

Thrush and bed sores are cited as two conditions, but perhaps respiratory infections are the most important complications, the prevention of which would result in a lower mortality rate. Frequently, following treatment, progress is satisfactory for a short time; but the occurrence of a head cold, with the possible subsequent development of bronchitis or broncho-pneumonia, brings about a fatal issue. Other complications are those referable to the gastro-intestinal tract, the commonest one being dyspepsia.

### *Diagnosis*

The diagnosis is usually easily made in well-marked cases; very few conditions showing a subnormal temperature.

### *Differential Diagnosis*

- Tuberculosis.
- Untreated cases of Congenital Syphilis.
- Syphilitic Hydrocephalus.
- Pyelocystitis.
- Congenital Heart Disease.
- Pyloric Stenosis.

*Course*

In most cases the course is steadily downward, but it may be cut short at any time by an acute disease. Frequently these infants die suddenly when apparently there is no sign of any definite recurrence of symptoms; this is likely due to sudden myocardial failure. However, many cases recover, and this depends as much on the constitution of the child as it does on the therapeutic measures outlined by the physician.

*Treatment*

## Prophylaxis.

If the main principles of breast and bottle feeding are adhered to the condition rarely develops. The chief problem is to supply a suitable food with sufficient caloric value, without overstepping the tolerance of the infant.

The main principles in treating a case are:

1. Maintenance of body temperature. This necessitates a warm room at a temperature between 70° and 90° F., and light but warm clothing.
2. Conservation of energy. The baby requires rest and quiet, should not be handled unnecessarily, and should be fed and cared for with the least possible expenditure of energy on the part of the patient.
3. Administration of fluids. Water is essential and should be offered frequently by mouth. The parenteral administration of fluid by hypodermoclysis, intravenous injection, or intra-peritoneal injection, is often necessary to combat dehydration. Simple transfusion of whole blood, 15 c.c. per pound body weight, is frequently of great value, not only to combat the dehydration, but also to better the child's general condition.
4. Baths should be reduced to one a week, an olive oil massage daily being substituted.
5. Prevention of parenteral infection. Nurses and doctors, when in attendance, should wear a mask over the nose and mouth in an attempt to prevent transmitting head colds to the infant.
6. Feeding. If obtainable Breast Milk is most useful. If Artificial Food is necessary, Lactic Acid milk with added carbohydrate as indicated or a mixture of Butter Soup  $\frac{2}{3}$  Whole Milk  $\frac{1}{3}$  are most suitable feedings. Both are high caloric, easily digestible feedings. Butter Soup should not be used where the child is suffering from a digestive upset, such as diarrhoea and vomiting.

*Prognosis*—Depends on the following factors:

1. The age of the infant.
2. The severity of the case.
3. The feeding administered.
4. The hygienic surroundings.
5. The prevention of complications.

*Summary*

1. Decomposition is a chronic state of malnutrition occurring in infants.
2. The chief etiological factor is improper feeding during the early months.
3. Few pathological changes are found at autopsy, congestion in the liver being the most constant.
4. Progressive loss in weight, emaciation and dehydration, diminished tolerance for food and lack of resistance to infection are the chief characteristics as seen clinically.
5. Treatment is often unsatisfactory—prevention of infection, conservation of energy, the parenteral administration of fluids and suitable feedings are the chief indications.
6. Prognosis depends chiefly on prevention of infection and the infant's ability to assimilate the food given.

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**OXYGEN DEBT**

J. M. D. OLMSTED, M.A., PH.D.

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The scientist is continually being called upon to justify his pursuit of so-called "pure science." "Of what practical use is it?" he is asked. One would certainly think that the frog-jumping experiments of elementary physiology could never have any practical application to human affairs, but Professor A. V. Hill has recently shown that from the results of such experiments a young athlete can gain valuable information as to the speed with which he can run or swim a given distance. It seems a far cry from a study of fatigue in a frog's gastrocnemius to picking a winner on Field Day, but nevertheless there is a most obvious connection between the two when once it is pointed out.

The measure of the physiological expenditure in any effort can be expressed as the amount of oxygen needed for that effort, since the energy expended is proportional to the extent of the oxidative processes which furnish the energy. The oxygen is supplied to the tissues where the energy changes are taking place *via* the arterial blood. That fraction of the oxygen of the arterial blood which is taken up by a tissue in the change from arterial to venous blood is called the oxygen utilization coefficient. If in a given organ, *e.g.*, the brain at rest, the arterial blood contains 20 per cent. of oxygen, and the venous blood 16 per cent., then 1/5th of the oxygen has been removed, and the coefficient is 0.2. During activity the coefficient of the brain rises only to 0.32. For muscle at rest the average coefficient is 0.4 and when stimulated, 0.8 to 0.9. If calculation is made on the basis of oxygen consumption, then for a man weighing 70 kilograms, the oxygen consumption when at rest is 300 c.c. per min., and during violent exercise, such as running a race, it rises to a maximum of 4000 c.c. per minute. To bring about this extra oxygen consumption there is not only an increase in the oxygen utilization coefficient in the muscles and other tissues, but the pulse rate is increased two and one half times, and also the output of the heart

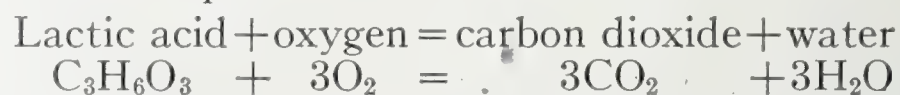
is increased; thus carrying the oxygen to the tissues faster and in greater quantities than when the individual is at rest.

But now comes the interesting fact that a degree of muscular effort can be maintained for a long period which demands an oxygen supply far in excess of even this increased oxygen utilization. The oxygen necessary for the effort may be supplied after the effort has ceased—in other words, the individual may run into debt for oxygen. The truth of this statement is evident when we realize that often in the 100 yards dash the runner holds his breath throughout the race for the advantage he gains in holding his chest rigid.

From the studies on frog muscle it has long been known that muscular exercise results in the production of lactic acid, an accumulation of which leads to fatigue and eventually to the inability of the muscle to contract at all. We know also that the act of contraction does not involve an oxidative process, but that during the "recovery period", which goes on for several seconds or even minutes after the contraction is over, approximately 1/5th of the lactic acid is oxidized and the remainder is transformed back into glycogen. Does this scheme apply to man?

When exercise commences the oxygen intake of man rises from the low resting value of 300 c.c. per minute to a high value characteristic of a given effort. In the case of an athlete running a race the maximum appears to be 4000 c.c. per min. This rise takes place within 2 minutes, in fact it almost reaches its maximum in 90 seconds. Lactic acid is being produced by the muscular effort in such quantities that it cannot be dealt with on the spot, but diffuses out from the muscle and is carried away in the blood stream. In a resting person there is found 5-20 mg. of lactic acid in 100 c.c. of blood, but after severe exercise for 10 minutes it has been found to be as high as 204 mg. Therefore at the end of the period of violent muscular exercise there should be an accumulation of lactic acid which a delayed "recovery process" must now remove. If we follow the oxygen consumption of the individual after the exercise we find that it may take as much as two hours to fall to its resting value. If, for example, the exercise lasted one minute, and during this time 4 litres of oxygen were used, during the next two hours 10 litres in excess of the resting requirement might be consumed. This would mean that the total effort demanded 14 litres of oxygen, 10 of which were not supplied until the exercise was over—an oxygen debt of 10 litres. Now the maximum oxygen debt a trained athlete can run up is 15 litres. If, therefore, an athlete is to be a record breaker he must, in all except the shortest races, be able to finish a race with nearly the maximum oxygen debt. This ability to run up an oxygen debt of 15 litres, skill in using his muscles and perfect co-ordinating powers of his nervous system are the essential qualities of an athlete who would establish a world record.

How does this 15 litre oxygen debt check up with the frog experiments? From the equation



it is evident that to remove completely by oxidation 1 gm. mol. or 90 gms. of lactic acid, 3 gm. mols. of oxygen are necessary. 3 gm. mols. of oxygen occupy  $3 \times 22.4 = 67.2$  litres. Since only 1/5th of the

lactic acid is burned, for each 67.2 litres of oxygen  $5 \times 90 = 450$  gms. of lactic acid should disappear. 15 litres of oxygen will, therefore, correspond to 99 gms. of lactic acid. If our athlete has done his best he should have an accumulation of practically 100 gms. of lactic acid in his body at the end of a race.

Earlier experiments on frog muscle by Fletcher and Hopkins showed that when an isolated muscle was fatigued in an atmosphere of nitrogen lactic acid accumulated to the amount of 0.2 per cent. If the muscle was now caused to go into rigor, either rigor mortis, or heat or chloroform rigor, double this amount or 0.4 per cent. was found. Later estimates have shown that 0.34 per cent. of lactic acid may accumulate before the muscle fails to contract through fatigue; and Meyerhof, stimulating the frog's gastrocnemius in a buffered Ringer's solution, containing more  $\text{Na}_2\text{CO}_3$  and  $\text{NaHCO}_3$  than usual, has been able to find as much as 0.5 per cent. before the muscle became fully fatigued. In all these experiments isolated muscles were used. Had the muscle been fatigued *in situ*, i.e., in the body with circulation intact, the results would have been more comparable to a man running a race. However, the conditions of Meyerhof's experiments resemble more closely the natural conditions than did the others, so that we may accept provisionally his figure, 0.5 per cent., as the maximum accumulation of lactic acid in muscle.

The muscles of our 70 kilogram athlete will weigh approximately 25 kilograms. In a state of utter exhaustion at the end of a race, when his muscles are so fatigued that they can no longer respond to stimulation, we could imagine that  $0.005 \times 25000 = 125$  gms. of lactic acid might be present in his muscles. It is extremely unlikely that this could ever occur. But we can see that an accumulation of 100 gms. of lactic acid, corresponding to the maximum oxygen debt of 15 litres. is quite possible; for even if all the lactic acid were contained within the muscles it would amount to only 0.4 per cent.; and as we saw above, much of it would escape into the blood stream, so that there would be a large margin of safety, and there never would be a sufficient amount of lactic acid to result in utter exhaustion.

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### WILLIAM BEAUMONT AND ALEXIS ST. MARTIN\*

W. MCKEE MASTER, '28

Up to the time of William Beaumont there had been various theories as to the progress and chemical nature of digestion. These theories were based on concoction, putrefaction, fermentation and maceration, and were being threshed out and discussed, but very little progress was being made, due to it being extremely difficult to procure gastric juice in its pure form or to get precise knowledge as to the stomach movements. As for the above theories William Hunter remarked: "Some physiologists will have it that the stomach is a mill, others that it is a fermenting vat, others that it is a stewpan, but in my view of the matter it is neither a mill, fermentation vat nor a stewpan, but a stomach, gentlemen, a stomach."

\*Abridged from the original second prize essay in History of Physiology, 1924-1925.

Preceding the works of Beaumont there had been some very important additions made to the physiology of digestion by the ingenious experiments of Reamur, Spallanzani and Stevens. These men had placed the theory of chemical solution on a sound basis, whereas the studies of Tiedemann, Gmelin and Prout had done considerable to solve the problems of the chemistry of the gastric juice. There was an enormous amount of uncertainty, however, as to the phenomena occurring during digestion in the stomach, the precise mode of action of the secretion, the chemistry of the juice and its action outside the body. On all these points the keen observations of Beaumont brought clearness and light where there had previously existed the greatest obscurity.

William Beaumont was born on November 21, 1785, at Lebanon, being the descendant of a long line of distinguished ancestors whose names were very prominent in the annals of French and English History since the time of William the Conqueror. As to William's very early life there appears to be no records. At the age of fifteen, however, he was a very studious lad. Urged by the feeling of restless ambition which seems to have pervaded his whole life and, by a desire to enlarge his field of usefulness, he left his father's home in the winter of 1806, without any particular destination. He taught school at Champlain, in New York State, for several years; and this early frontier life, along with his previous training, moulded Beaumont into a man of excellent character.

In 1810 he went to St. Albans, Vermont, apprenticing himself to Dr. Benjamin Chandler, a very prominent and capable practitioner. In this choice Beaumont could not have been more fortunate as Chandler instilled into the mind of his young pupil from the start the importance of developing his memory, his powers of observation, and the habit of logical thought. Beaumont in turn prepared powders, mixed concoctions, made the pills, swept the office, cleaned bottles, assisted in operations, and often through main force supplied the place of the anaesthetic of to-day in the amputation of limbs and other surgical operations. Nothing could have foreshadowed the coming events of Beaumont's life as the case histories contained in his note-book. They serve to demonstrate very conclusively that the power of keen observation and true scientific spirit were manifest in him at an early age of his career, that the nucleus was there and all that it required was proper encouragement, which truly was given by Chandler. Beaumont worked through his apprenticeship, improving every day, reading masters, dissecting when opportunity offered, attending post mortems and finally in June, 1812, received his license to practise.

Shortly after receiving his license the War of 1812 broke out, and young Beaumont, as surgeon's mate in the army, served in many engagements and received special mention for his cool bravery and fidelity to his duties. When the war ended Beaumont practised his profession at several places always winning a high esteem for himself from those with whom he came in contact.

In 1820 Beaumont accepted a commission as past surgeon in the army, this having been given to him by the Surgeon-General, Dr. Jas. Lovell, who had a very high regard for Beaumont's ability. He was stationed at Fort Mackinac, the centre of a series of fur trading posts

on the northwestern frontier, and while there Beaumont grasped the opportunity of imprinting his name, in conjunction with Alexis St. Martin, upon the pages of history of physiology.

In June, 1820, a French-Canadian, Alexis St. Martin, was shot at close range, leaving a cavity in his left upper abdomen that would admit a man's fist. A description of the wound is best given by Beaumont's own hospital records as follows: "The entire charge, consisting of powder and buckshot, was received in the left side at not more than two or three feet distance from the muzzle of the piece, in a posterior direction, obliquely forwards and outwards, carrying away by its force the integuments more than the size of the palm of a man's hand, blowing off and fracturing the sixth rib from about the middle anteriorly, fracturing the fifth, rupturing the lower portion of the left lobe of the lungs and lacerating the stomach by a spicula of the rib that was blown through its coat lodging the charge, wadding, fire in among the fractured ribs and lacerated muscles and integuments, and burning the clothing and flesh to a crisp. Found a portion of the lungs as large as a turkey's egg protruding through the external wound, lacerated and burnt, and below this other protrusions resembling a portion of the stomach, although hard to believe it as such and the patient still living with a puncture in the protruding portion large enough to receive my forefinger." Beaumont goes on with a minute description of the wound, treatment and resistance of the patient, demonstrating again the precision with which he kept his medical histories.

Beaumont attended St. Martin almost continuously for two years, at the end of which time the patient was able to walk and help himself to a slight extent. It was not until 1825 that Beaumont realized the wonderful opportunity for research which had been placed in his hands. He communicated with Lovell and then began a series of experiments on the gastric juice and digestion under the most adverse conditions possible, with no facilities for research or even a physician within a radius of many hundred miles from whom he could receive suggestions. Beaumont secured a transfer from Mackinac to Fort Niagara in order to carry on the experiments under better conditions, but soon after this move Alexis took "French leave" of his benefactor.

At this time Beaumont had completed four experiments, the nature of which will be described later amongst his works. He now compiled his experiments to date and published them in the Medical Recorder, and by so doing he became known and recognized over the continent for his excellent opportunity to study and his knowledge of the processes of digestion.

The doctor was transferred to Green Bay, and while here St. Martin was found and persuaded to return in order that experimentation might be continued. Beaumont resumed the work exactly where he had left off, namely, determining the temperature of the stomach under varying circumstances and conditions. After concluding these he commenced investigating on several new series of experiments carefully noting minutely, exactly what he observed, all of which is recorded in his book. Beaumont, accompanied by St. Martin, went to Washington, and by March, 1833, he had concluded one hundred and sixteen experiments. Soon after this St. Martin left to visit his family in Canada, never to

return again to Beaumont, although the latter tried consistently in later years to procure his ungrateful man Alexis, to whom he had been so kind and generous.

Beaumont's research on the digestive processes had made him widely famed by now and had brought to him several honours, along with requests, that he publish an account of his experiments to date. These works he compiled and in 1833 published his book, "Experiments and Observations on the Gastric Juice and the Physiology of Digestion," which is, without doubt, the most authoritative reference on this subject even up to the present day. In his book Beaumont has recorded his observations in the true spirit of inquiry and submitted a body of facts which cannot be invalidated even though his opinions possibly may be doubted or denied.

To describe fully the results of works given in Beaumont's book would be impossible in this essay, so the writer will outline his most outstanding pieces of research enumerating them in order that they will be as concise as possible:

•Animal and farinaceous aliments are more easy to digest than vegetable.

The ultimate principles of aliment are always the same from whatever food they may be obtained.

The digestibility of the aliment does not depend upon the quantity of nutrient principles that it contains.

The time required for the digestion of food is various, depending upon the quantity and quality of the food, state of the stomach, etc., but the time ordinarily required for the disposal of a moderate meal is from three to three and a half hours.

Solid food, of a certain texture, is easier to digest than fluid.

The use of ardent spirits always produce disease of the stomach if perverted in.

The natural temperature of the stomach is one hundred degrees Fahrenheit.

Exercise elevates the temperature and sleep or rest lowers it.

The agent of chymification is the gastric juice.

It acts as a solvent of food and alters its properties.

It contains free muriatic acid and some other chemical principles.

It is never found free in the gastric cavity, but is always excited to discharge itself by the introduction of food or other irritants.

It is secreted from vessels distinct from the mucous follicles.

If obtained when pure it is capable of being kept for months.

It coagulates albumen and afterwards dissolves it.

That pure gastric juice is fluid, clear and transparent, without odour, and a little salt and perceptibly acid.

It is capable of combining with a certain and fixed quantity of food and when more aliment is presented for its action than it will dissolve, disturbances of the stomach and digestion will ensue.

Chyme is homogeneous but variable in colour and consistency.

Towards the later stages of chymification it becomes more acid and stimulating and passes more rapidly from the stomach.

Water, ardent spirits and other fluids pass from the stomach soon after they have been received.

The inner coat of the stomach is pink in health, sheathed with a mucous coat.

The motions are in two directions, transversely and longitudinally.

The expulsion of the chyme is assisted by a transverse band.

Beaumont synopsised tables of articles of diet and their mean time of chymification which are even to-day the basis and reference for dietetics. He demonstrated the profound influence of mental disturbances on the secretion of the gastric juice and on digestion. Thus by the above results it will be seen that Beaumont made no hypotheses, but drew conclusions from his actual observations unbiased by any previous experimentalists' views on digestive processes. True, Beaumont made a number of conclusions which have to-day been disproved, but these were not due to him attempting to propound any new theories but due to a misinterpretation of his observations.

After publishing this volume which practically revolutionized the knowledge of the processes of digestion of that time, Beaumont was moved several times, and finally posted at St. Louis. Here, arriving as he did with a well-established reputation as an army surgeon, and the prestige given him through publication of his book, along with his strong personality and splendid presence, private practice fell into his hands very readily, and within a year he had a large, lucrative practice. In 1840 he resigned from the army due to some trouble with a new regime, and settled down to a private practice enjoying the society of a host of devoted friends and an affectionate family. In March, 1853, Beaumont sustained a violent blow on the back of his head from a fall, and a few weeks later died at the age of sixty-eight.

As for Alexis St. Martin, who had contributed so much to science, on account of an unfortunate accident to himself, he had wandered from place to place always in abject poverty because of his loose character. He finally settled in St. Thomas de Joliette, Canada, and died in 1880 at the age of eighty-one.

In summing up, Beaumont was the pioneer physiologist of North America, being the first to make an important and enduring contribution to this science. His work remains a model of patient, persevering investigation, experiment and research and the highest praise one could give him would be to say that he lived up to, and fulfilled, the ideals with which he set out. These ideals he expressed by saying: "Truth, like beauty, is when unadorned, adorned the most."

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#### **American Board of Otolaryngology**

An examination will be held by the American Board of Otolaryngology in Dallas, Texas, on Monday, April 19, 1926, and in San Francisco, California, on Tuesday, April 27, 1926.

Application should be made to the Secretary, Dr. H. W. Loeb, 1402 South Grand Boulevard, St. Louis, Missouri.

**CHORIONEPITHELIOMA**

W. H. HATFIELD, '26

*Definition.*—A malignant tumor which develops from the epithelial elements of the placental tissue.

*Etiology.*—It was first described by Saenger in 1892. He believed that the tumor developed from decidual cells of the endometrium and gave the name deciduoma to the disease, supposing it to be a sarcoma. Later Marchand described the histology more exactly, and showed that the tumor growth develops from the epithelial cells surrounding the chorionic villi, and is therefore a carcinoma. He suggested the name chorionepithelioma. Through the work of Marchand, Aschoff and Teacher the origin of these growths from foetal epiblast is generally recognized (1).

The tumor may arise after normal parturition, abortion, expulsion of hydatidiform mole and in extra uterine gestation. Although most commonly related to pregnancy, etc., quite a number of cases have been described in which such relationship could be entirely excluded. Most of these occur in the male, and are nearly all of testicular origin, arising in relation to teratomatous new growths. Parkes Weber (2) reports a case occurring in the male, the tumor occurring at the bifurcation of the abdominal aorta, with numerous tumors scattered throughout the liver. Occasionally the tumor shows itself first not in the uterus but in some other situation, such as the vagina, brain, liver, lungs or kidneys (3). Blair Bell believes that a malignant neoplasm in the human subject is a biological atavism. In discussing chorionepithelioma (4) he states "that there is a time in the development of the ovum when somatic cell correlation and differentiation can hardly be said to exist except potentially. At that early stage the trophoblast is engaged in a struggle for existence. The zygote possesses the power of developing into cells of two types, the undifferentiated nutritive cells and the differentiated somatic cells. Normally, when satisfactory attachment has been obtained, the area in which the foetus is to develop grows, and the activities of the trophoblast, as far as plastic and invasive properties are concerned, are gradually arrested. Should the foetus die, and the supply of somatic 'correlating secretion' cease, at a critical time in the period of control the chorionic epithelium, suddenly relieved of the inhibitory reaction of this substance, may develop into that most unrestrained and malignant manifestation known as chorionepithelioma."

The average age, according to Teacher, for the development of chorionepithelioma is thirty-three. It is one of the rare forms of neoplasms. About 50% of all cases follow hydatidiform mole, but only about 2% of hydatidiform moles become malignant (5). Some writers estimate it much higher, e.g., Findlay, after a study of 500 cases, concluded that 26.2% of hydatidiform moles become malignant (6). The general trend of opinion seems to be that the percentage is very low, even 2% being somewhat high.

*Pathology.*—Two facts are worthy of preliminary emphasis.

(1) The histological elements in hydatidiform mole and chorionepithelioma are identical with those seen in normal tissue.

(2) Even the normal trophoblast is a distinctly invasive tissue, the malignant choriomatous tumors differing from it only in degree.

In order to understand the microscopic appearance of chorion-epithelioma it is necessary to briefly review the histology of the chorionic villus from the epithelial elements of which chorionepithelioma has its origin.

The normal chorionic villus consists of a case of mesoderm, covered with a variable layer of ectoderm, depending on its stage of development (7). There is a double epithelial layer, the superficial being known as the syncytium, while the deeper consists of a cellular layer, the cells of Langhans. The syncytium, as the name implies, is not marked off in cells but is more or less a continuous layer of cytoplasm in which the nuclei lie. In the deeper layer the cell boundaries are quite distinct, and each cell contains a single large ovoid nucleus. From the seventh month of pregnancy to full term, the syncytium becomes thinned and even completely disappears from considerable portions of the villi, being replaced by canalized fibrin. At other points the syncytial cytoplasm becomes much thickened, and the nuclei appear to be bunched or grouped within the thickened portions; these areas are known as cell knots or proliferation islands.

*Macroscopic Appearance.*—The tumor usually begins in the chorion frondosum, but may arise from any part of the uterus to which chorionic villi are attached. It occurs in the form of solid purplish red nodules, mottled with pale areas, frequently haemorrhagic and is soft, friable and spongy. It tends to form polypoid or fungating growths, projecting into the uterine cavity, but eventually invades the surrounding muscle. The tumor masses may be single or multiple. The malignant chorionic elements show the same tendency as the normal chorionic epithelium, to travel into and along the blood vessels, which fact explains the haemorrhage which forms a characteristic histological feature of the tumor as well as its mode of spread (8). Venous extension may occur down to the vagina, where secondary bleeding masses of tumor may be found. The vagina is involved in about one half the cases (9).

*Microscopic Appearance.*—The tumor, as has already been said, originates in the syncytium and Langhans layer of the chorionic villi. The normal relations are disturbed, the syncytium is thickened and the cells of Langhans layer tend to extend through the surface. The so-called syncytical elements are large, irregular or elongated plasmodial masses containing numerous deeply staining nuclei. The protoplasm is finely granular and may contain vacuoles. The cells derived from Langhans layer form groups of varying size, are irregular, long, spindle or spherical-shaped, with pale protoplasm, and the nuclei often show mitosis. In some cases the cells of Langhans are grouped around the plasmodial masses, but in other cases the latter are in excess, and arranged in more or less parallel rows, with their long axis at right angles to the base of the tumor (10). There is no regular stroma or blood vessels, the cells deriving their nourishment from the blood with which they are so abundantly bathed (11).

There is no absolute indication of malignancy by microscopic examination. Hitschmann and Crestogollette came to the following conclusion: "We are convinced that a histological difference is improbable,

and we know of absolutely no morphologic or biologic difference between physiologic foetal tissue and pathologic. The more carefully we study the earliest phases of placenta formation, and compare them with chorion-epithelioma, the more we feel justified in the statement that between trophoblast (foetal) and chorionepithelioma there is no difference."

Marchand, Aschoff, Zagorianski, Kissel, V. Frangue, Abrecht, Hormann and others agree that we have absolutely no histological criterion for determining the malignancy of these tumors.

An attempt has been made to classify the chorionic tumors—Two classifications will be mentioned here:

#### I. TEACHER:

- (1) Simple hydatiform moles.
- (2) The malignant or destructive hydatidiform mole.
- (3) The pure chorionepitheliomata showing no chorionic villi.
- (4) A group between the last two consisting for the most part of chorionepithelium, but showing some evidence of villi.

#### II. EWING:

- (1) Hydatiform mole.
- (2) Chorio adenoma destruens.
- (3) Chorio carcinoma.

Statistics show that choriomatous tumors have frequently associated with them multiple lutein cystic conditions of the ovaries. The lutein cells are probably of the type of thecalutein cells, and the process is merely an exaggeration of what happens during normal labour. Presumably the stimulus for the formation of the thecalutein cells emanates from the embryo, probably the trophoblast, and it would seem that with hydatidiform mole or chorionepithelioma the trophoblastic overgrowth is responsible for an enormous increase and perhaps perversion of this causative stimulus, so that the ovarian response is correspondingly increased (12).

*Symptoms.*—The chief symptom is uterine haemorrhage following abortion, full time labour or hydatidiform mole. In some cases it follows almost immediately after the termination of pregnancy or occurs during pregnancy itself. In other cases it is delayed even over a year as occurred in eight of Teacher's cases. Bleeding is not an invariable symptom in the early stages, and even amenorrhoea may occur, as in a case reported by Caturani.

As soon as necrotic changes begin to take place in the tumor offensive vaginal discharge occurs. It is likely to be thin and watery and brownish or bloody in appearance.

Pulmonary symptoms due to metastasis occur fairly frequently—pain, blood-stained sputum and cough.

Pain in the lower abdomen and small of the back may be present. The later stages are marked by progressive weakness, anaemia, rigors, emaciation and gradually increasing pelvic pain.

*Signs.*—In about one half the cases the first indication of the tumor is the appearance of vulvar or vaginal metastases, situated most frequently in the anterior vaginal wall and having a rather characteristic dark bluish varix. Bimanual examination shows the uterus slightly enlarged.

In advanced cases the solid plugs of tumor can be felt extending from the uterus to the side walls of the pelvis and vagina. Curettage brings only temporary cessation of bleeding, and a second attempt reveals a new mass of tissue in the cavity of the uterus. Albuminuria is a frequent accompaniment.

*Differential Diagnosis.*—This is often difficult. The main difficulty arises in early cases. After metastases have occurred the diagnosis is usually quite simple but it is then usually too late for treatment.

Conditions to be considered are:

- (1) Retained products of pregnancy.
- (2) Chronic endometritis.
- (3) Mucous polypi.
- (4) Fibromyoma.
- (5) Cancer.
- (6) Sarcoma.

The latter five are excluded by a careful examination of the history and signs and by microscopic evidence derived from curettage. In the case of retained products of pregnancy microscopic examination of the curetings is of aid in well-defined cases. Cureting, as a rule, produces a cure in these cases, whereas in chorionepithelioma it does not.

As stated before, there is no histological criterion for determining the malignancy of these tumors.

*Treatment.*—In 1896 Apfelstaedt stated that therapy against these most malignant of all known neoplasms was madness. Nevertheless six years later Polano reported 50% and Teacher 63.3% of cures (13). The first instances of spontaneous cures were reported by Pick and Schlagenhauer, the latter concluding from observation of his case that there were two forms: the first extraordinarily malignant and the other benign from the start.

Curettage is dangerous and worthless in diagnosing chorionepithelioma (14). If in removing an hydatidiform mole, chorionepithelioma is suggested hysterectomy should follow. It is often difficult to decide when to operate. If radical operation is done there is a chance that the patient will be subject to needless dangers with also the loss of the organs. If one does not operate and waits for later symptoms to develop, metastases may take place and it will be too late to save the patient.

If the initial curetings show a large number of grouped Langhans and syncytial cells, immediate operation is advisable, especially if a hydatidiform mole has preceded. If the symptoms have followed abortion, it is justifiable to wait to see if further bleeding ensues. If after careful cureting of a suspicious case bleeding recurs and the curetings again show the same findings, radical operation is indicated. It is unnecessary to do a Wertheim's operation, as the glands are rarely, if ever, affected (15). One should completely remove the uterus and any metastatic growths in the vagina, labia and other accessible parts. Regression of chorionepithelioma has been observed (16). Both primary tumors and metastasis may regress and cures have resulted after incomplete removal.

T. J. Watkins has suggested the advisability of applying radium as a prophylactic after the removal of a mole.

A great deal of work has been done lately on the treatment of these, as well as other malignant tumors, by the use of lead administered intravenously. Blair Bell (17) found that lead had an affinity for phosphatides and other lipins, and that these substances are present in malignant growths in larger quantities than in normal somatic tissue. The quantities of phosphides and the phosphatide cholesterol ratio in chorionepithelioma was found to be greater than in any other tissue. Lewis (18) found that a high lecithin phosphatide ratio indicates a high degree of permeability of the cell membranes. Therefore chorionepithelioma has an increased affinity for lead, and its cells have a high degree of permeability, and so the lead treatment may yet yield something of great value in the treatment of this condition. Its only drawback at present is the toxic influence of lead on the other organs of the body. Partially colloidal solutions have been found to be less toxic than ionic solutions. At present a method is being sought by means of which the metal may be locked in the neoplastic tissues by calcium administered intravenously in a colloidal form after the patient has received as much lead as he or she can tolerate. The principle is that calcium salts decrease the permeability of the cell membrane (19).

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### THE ORIGIN AND DEVELOPMENT OF THE THEORY OF ELECTROLYTIC DISSOCIATION

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The theory of electrolytic dissociation has exerted a profound influence on the development of chemistry during the last forty years. Indeed it is well nigh impossible to read intelligently any modern paper on physical or biological chemistry without a working knowledge of this theory. A number of medical students have assured the author that in their studies of physiology and the various branches of biological chemistry they come in such close contact with the theory as would justify a few remarks on the subject in an undergraduate medical

journal. I propose then below to say a few words regarding the origin and development of the Theory of Electrolytic Dissociation in Solution.

There have been two principal roads which have led to views related to the modern theory of electrolytic dissociation. The first takes its origin in the law of so-called additive properties of salt solutions. Valson's (1870) work on the height to which salt solutions rise in capillary tubes was among the earliest investigations to demonstrate this law, and his results will serve to illustrate the general law.

He found that the difference of the property under investigation (here capillary height) between a chloride and a nitrate is "the same for the potassium salts as for the sodium, or lithium, or calcium salts." The capillary height might then be "conveniently calculated as the sum of three components, the one the capillary height of pure water, and the other two corrections which should be added, the one for the positive radical of the salt and the other for its negative radical." Continuing, Valson says "Experience shows that the effects of capillarity are nearly proportional to the quantity (concentration) of the examined substance, but this is not true for concentrated solutions, in which the actions of the molecules are not independent of each other. It therefore seems that it is necessary that the saline molecules occur in a medium of sufficient volume, in order that they may be regarded as having reached the state of liberty." Following hard upon Valson's work it was soon shown that the law of additivity held for a great number of physical and chemical properties.

Raoult summarizes all the work of this nature in a notable memoir in 1885: "Then, the diminishing of the capillary heights, the increase of the densities, the osmotic pressure, the lowering of the freezing point, briefly most of the physical effects produced by salts on the water dissolving them are the sum of effects produced separately by their constituent electropositive and electronegative radicals, which act as if they were simply mixed in the liquid." Raoult also points out and tries to explain the fact that the additive law does not hold for concentrated solutions nor for solutions of weak acids such as hydrocyanic and acetic acids.

It is just this additivity of the chemical properties of dilute solutions which is the basis of our methods of analysis, since the distinctive characteristics of salts in solution, upon which qualitative analysis is almost exclusively based, are the simple additive properties of their ions. One can then do without the knowledge of the individual properties of salts in order to distinguish them from each other, on condition of knowing the analytical properties of their ions.

For example, in the analysis of a substance (say a mixture of silver nitrate and copper sulphate) the first operation is to dissolve the solid in water, after which we follow a scheme for separating and testing for the ions present in the solution. In the case in question such an examination of the above solution would find silver ion, copper ion, nitrate ion and sulphate ion present. The analyst would, however, be quite unable to tell whether his solution had been made from a mixture of silver nitrate and copper sulphate or a mixture of copper nitrate and silver sulphate. To answer such a question some procedure very different from that ordinarily used in qualitative analysis would be necessary.

Indeed, no study of the solution in water has ever answered this question since solutions made from silver nitrate and copper sulphate are found to be identical with (*i.e.*, quite indistinguishable from) solutions made from silver sulphate and copper nitrate.

The second road which has led to the theory of electrolytic dissociation takes its origin in the study of the passage of electricity through salt solutions. Faraday, Kohlrausch, Williamson and others had been studying the electrical conductivity of dilute solutions. In 1884 Arrhenius set forth his theory of all these experiments: "Solutions of electrolytes contain two different kinds of molecules, of which one is a non-conductor, the other (called active molecules) a conductor. The number of active molecules increases with the dilution at the expense of the inactive ones." Thus from measurements of electrical conductivity at various dilutions the degree of dissociation could be obtained, and so could be used in the interpretation of all the data on osmotic pressure, freezing-point depressions and other properties of aqueous solutions.

The definite enunciation of the theory of electrolytic dissociation was then first given by Arrhenius, though Arrhenius himself (see Arrhenius: *Theory of Solutions*, Yale University Press) points out that the ideas of this theory may be found in a less fully developed state long before his time. We should associate with the name of Arrhenius the names of those workers, a few of them mentioned above, who had accumulated sufficient experimental data to demand the explanation which Arrhenius gave. Also van't Hoff and Ostwald had a share in the elaboration of the theory itself.

There are a number of disconcerting weaknesses in the theory of dissociation. Strong electrolytes, which are of great importance in nature and the industries, have not been satisfactorily dealt with by the theory. There are, moreover, many solutions in solvents other than water which conduct very well and therefore appear to be highly dissociated but which give freezing-point depressions which indicate no dissociation.

Various modifications of the theory have been and are being made in the attempt to bring it into better accord with the behaviour of concentrated solutions. One of these is that the ions bind to themselves water. Washburn has had some success with such a theory. Another theory is that there is complete dissociation even in concentrated solutions, and that the peculiarities of these solutions can be explained by a consideration of the electric attraction of the charged ions on each other or on the water surrounding them.

Evidently the theory is far from explaining satisfactorily all the properties of even dilute solutions. It has however stimulated an immense amount of useful work, and has permeated chemical literature and left its stamp on chemical language in a remarkable way.

It is well to keep in mind that when a writer assigns a certain value as the "Hydrogen-ion concentration of the solution" he has in mind a certain measurement made on the solution. Possibly he has in mind its effect on the colour of some indicator: possibly a certain electromotive force measurement: possibly even the rate at which starch is hydrolysed or sugar inverted by the solution. His meaning can hardly be properly

understood unless the reader determine (and this is unfortunately not always possible) what experiment leads him to say his solution was at  $\text{pH}=4.6$ .

When our language becomes greatly abbreviated there is danger of misunderstanding. The author has been persuaded of this by the answers he has heard regarding the meaning of the much abbreviated expression " $\text{H}_2\text{O}$ ."

For a bibliography of references to the papers mentioned above see Arrhenius: *Theory of Solutions* (1912), Yale University Press.

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## TUBERCULOSIS IN INFANCY AND CHILDHOOD\*

D. S. BENNETT, '26 AND F. T. FRALICK, '26

About 400 B.C. Hippocrates described very accurately the clinical manifestations of phthisis, but regarded it as a suppurative process in the lung. Lesions of Pott's Disease have been found in an Egyptian mummy of the period of about 1000 B.C. Sylvius, in the middle of the 17th century, was the first to associate tuberculous nodules with phthisis, describing them as enlarged lymph nodes. Stark, in the latter part of the 18th century, described the tubercle accurately. Early in the 19th century Bayle recognized that tuberculosis was not limited to the lungs, but was a constitutional condition, and that tubercles could appear in any organ. About the same time Laennec taught that every case of phthisis developed from tubercles and therefore the two were identical. Numerous attempts to discover the essential virus were unsuccessful till 1882, when Koch described the tubercle bacillus.

### ETIOLOGY

#### 1. Incidence

Tuberculosis occurs in all parts of the world and affects many of the lower animals as well as human beings. No race is immune, although the disease is pre-eminently one of civilization. No age is exempt. The frequency of tuberculous infection increases steadily as age advances as is shown by the results of the tuberculin test. As an example we might quote recent results of the von Pirquet test at the Children's Hospital at Philadelphia, as found by Gittings in a series of 1219 patients. He found at 1 year, 15% infected; at 8 years, 42% infected; at 12 years, 80% infected. Many men report that at 25-30 years of age 100% of individuals are infected.

The age incidence of fatal tuberculosis shows a high death rate just after infancy and from 2-4 years of age. It is low from 10-15 years, and then there is a general rise in the death rate with the highest between 30-40 years or later.

All records show the death rate to be declining since 1865. In the United States the death rate from tuberculosis from 1881 to 1917 fell from 390 to 146 per 100,000. The decline is attributed to: (a) Amelioration of social conditions, *i.e.*, improvement in housing, dietetics, hygiene and sanitation, etc; (b) education of the public; (c) improved methods

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of treatment, including isolation and care of adults with tuberculosis; (d) gradual inheritance of an acquired immunity; (e) gradual elimination of the most susceptible subjects.

## 2. *Predisposing Causes*

These include all the conditions which bring about a diminished resistance of the body to tuberculous infection: (a) Hereditary susceptibility; (b) respiratory infections—measles, whooping cough, influenza; (c) infected tonsils and adenoids; (d) malnutrition—especially the child who refuses fat and milk, and is allowed to choose sweets and starches; (e) unsanitary surroundings—filth, lack of fresh air and sunshine; (f) overcrowding; (g) diabetes; (h) climate—cold and dampness.

## 3. *Exciting Causes*

Human beings are susceptible to two types of tubercle bacillus—human and bovine. The human type is responsible for nearly all pulmonary, meningeal, and bone and joint tuberculosis, while the bovine type is frequently responsible for tuberculosis of the abdomen and cervical glands.

## IMMUNITY

In experimentation with guinea-pigs it has been shown that a small dose of a pure culture of tubercle bacilli, injected subcutaneously, produces in 10-14 days a local ulceration which never heals, enlargement of the local lymph glands, and a general tuberculous condition, which kills the animal in 6-12 weeks. However, if a second small dose of bacilli is given one week after the first, there forms a local ulceration which heals quickly, permanently, and with no localized enlargement of glands, and the animal dies at a later date than if it had received only one dose. Usually it is impossible to reinfect the tuberculous animal by small doses administered in any manner. There is, however, a sensitiveness to reinfection with massive doses. Thus it is believed that mild tuberculous infections in childhood confer a certain amount of immunity against reinfection with the tubercle bacillus. On the other hand, a primary infection at any age, if massive, or frequently repeated before immunity is established, is apt to be severe. Many believe that tuberculous infection always occurs in childhood, and remains latent until the bodily powers of resistance are lowered either at puberty, parturition, lactation, as a result of malnutrition, etc.

## METHODS OF TRANSMISSION

### 1. *From "Open" Cases*

(a) By means of material from lungs and bronchi and mouth secretions of the consumptive which are coughed or sneezed and spread by droplet infection.

(b) By contamination of hands and toys of children with fresh sputum on pavement of streets, and floor dust in houses where careless consumptives live.

## 2. *From Infected Cows*

The bovine bacillus is transmitted to humans in the milk and milk products, and rarely, if ever, in the meat of such cows.

### MODES OF INFECTION

#### 1. *Inhalation*

Most authorities consider this to be the most important mode of infection. Ghon believes that in childhood the primary infection of the lungs represents the usual form of tuberculous infection and that it is always aerogenous.

#### 2. *Ingestion*

This is next in importance to inhalation as a mode of infection. The acid contents of the stomach have little or no effect on the tubercle bacillus, and so it passes directly to the small intestine. It has been proven that the bacillus can pass through healthy intestinal mucosa, through the mesenteric glands, and be recovered in the chyle of the thoracic duct. This gives a direct route through the blood stream to the lungs. Adami regards the lymphoid tissues of the intestinal mucosa as constituting the body's first line of defence against invading organisms, while the nodes draining the different areas are the second line of defence. Small doses of bacilli do not get past the first line of defence. Some maintain that the primary infection may occur through the mucosa of the mouth or through the tonsils, then to the cervical glands and finally to the lung. Contrary to this Gittings says there is no direct lymphatic path between the cervical glands and those of the pleura and tracheo-bronchial system.

#### 3. *Other Rare Modes of Infection are:*

(a) Inoculation of a wound, *e.g.*, a bite from a consumptive and from ritual circumcision.

(b) Intra-uterine—through a tuberculous placenta.

(c) From mother's milk. This occurs only when the mammary gland itself is diseased.

### PATHOLOGY

Under two years of age tuberculosis most commonly affects the lungs and bronchial lymph nodes. After two years, tuberculosis of bones, cervical and mesenteric lymph nodes, peritoneum, and intestines becomes more frequent. At autopsy almost every case of tuberculosis shows some lung involvement.

#### 1. PULMONARY LESIONS

##### *Primary Focus*

Ghon says there is a primary lung focus in almost every case of tuberculosis in childhood. He has shown that the primary lung focus is usually single, more frequently involving the right side and seldom both lungs. This predilection is explained by the existence of a shorter and more direct bronchial route on the right side, and the fact that the

dividing spur lies to the left of the median line. Usually the focus involves only one lobe, most frequently the upper one. It is more frequently sub-pleural than intra-parenchymatous. The size of the focus varies from the size of a pinhead to that of a hazel-nut. It is well defined, has a fibrous capsule, and consists of dry, hard or soft masses. The caseous tubercle may be converted into a cavity up to the size of a hazel-nut. If it tends to heal the tubercle petrifies. The larger group of cases in Ghon's series showed the lesion to be still progressive—the smaller group, some evidence of complete anatomical healing. As a rule he could trace out a small bronchus apparently ending in front of, or in the focus. In most cases of primary focus there is some pleural adhesion, always in relation to the focus. There is rarely a lung focus without tuberculous change in the tracheo-bronchial lymph glands, or elsewhere. There was no case in which the change in the lung foci was later than that in the adjoining lymph glands. Ghon concluded that in every case the change in the lymph glands was secondary to involvement of the lung.

(a) *Tuberculous Bronchopneumonia*

This is the most common and most characteristic form of tuberculosis in infants and young children, and in them is the type which most frequently causes death. It is not uncommonly the sequel to an attack of measles or whooping-cough. It is considered to frequently arise by aspiration from tuberculous bronchial lymph nodes. The process is more diffuse than in adults, but after the sixth or seventh year simulates more closely the adult condition. Both lungs are involved, one much more than the other. The upper lobes are more often affected than the lower, that part of the lobe near the lung root being especially involved. The course is usually somewhat subacute. The pleura is almost always affected. There may be simply dense connective tissue adhesions, or, in other cases, the pleura is greatly thickened and contains caseous deposits. The cut surface of the lung in the early stages shows small gray or yellowish-white caseous nodules, or larger caseous areas which have already undergone softening. These areas are usually arranged around the bronchi. Microscopically they appear as tuberculous deposits in the walls of the small bronchi. About each focus there forms a zone of simple bronchopneumonia. By the extension of the process from the various affected bronchi and the coalescence of these lesions, large areas may become involved. An entire lobe may be involved, but more often there are smaller areas in several lobes. Softening and excavation then occurs in the centres of the caseous areas, leading to the formation of ragged cavities containing caseous masses or pus. In infancy there is little or no tendency to fibrosis about these areas, the process being continuous until death of the patient. In older children the progress is usually less rapid and interrupted by intervals of arrest or partial retrogression.

(b) *Miliary Tuberculosis*

This is often a part of general tuberculosis, although the lesions may be most extensive in the lungs. Both lungs are usually involved. The tubercles are found in the parenchyma of the lung, in the connective tissue forming the septa, along and in the walls of the bronchi and blood

vessels, and in the visceral pleura. They may be scattered singly through the lung or aggregated in groups, even so close together as to render that part of the lung nearly solid. Some are very small and transparent, others are larger and more opaque, and may contain a lighter centre due to necrosis. The intervening lung tissue in some places may appear quite normal. In other parts it is congested and presents the lesions of simple bronchopneumonia. There is also an acute bronchitis of the small and middle-sized bronchi. The miliary tubercles in the lungs are of the same structure as those formed elsewhere, although the filling of the alveoli with exudate makes the lesion appear more complex.

(c) *Chronic Phthisis*

In young children, and especially in infants, no condition is found resembling chronic tuberculosis in older children and adults. The nearest approach to this condition is seen in the cases of tuberculous bronchopneumonia, which run a slow, irregular and somewhat chronic course. The pathological process in these patients consists of a chronic interstitial bronchopneumonia with tuberculous nodules, which are old, and are for the most part converted into dense fibrous tissue, in the centre of which, however, some softened caseous areas may be seen.

## 2. TUBERCULOUS PLEURISY

Tuberculous pleurisy without tuberculosis of the lungs or of the bronchial glands is of doubtful occurrence.

(a) *Dry Pleurisy*

In this form there may be only an exudation of fibrin, or the pleura may be covered with gray tubercles and yellow tuberculous nodules. Great thickening of the pleura may take place.

(b) *With Effusion*

In infants tuberculosis does not produce pleural effusion. In older children it is uncommon, and when it occurs it usually acts as a primary disease. The pathological process is the same as in the dry form, except that serum is produced and may be enclosed in sacs due to the adhesions.

## 3. TUBERCULOUS MENINGITIS

This is the most frequent form of meningitis in young children. It occurs chiefly in the first two years of life. In Holt's series this was the cause of 40% of deaths from tuberculosis. Dr. Erb reports at the H.S.C. that of 50 deaths in cases of mediastinal tuberculosis 33 died of meningitis. The lesions involve the pia mater of the brain and sometimes that of the cord. It is usually only a conspicuous lesion of acute miliary tuberculosis, and it is doubtful if it ever occurs in the absence of a tuberculous focus. Most commonly the pathological lesions are found as miliary tubercles along the vessels, usually at the base, but when numerous are over the convexity also. The inflammatory products are most abundant at the base. There is usually only a small amount of fibrin and pus. There is almost always excess of fluid in the ventricles, sometimes amounting to actual hydrocephalus. This is due to blocking of the foramina of Magendie and Luschka, or aqueduct of Sylvius, or

inflammation of the ependyma of the choroid plexus. In prolonged cases, due to the increased pressure in the ventricles, there may be flattening of the convolutions: in infants, bulging of the fontanelles and even separation of the sutures. In severe cases the cortex below the affected pia shows congestion and superficial encephalitis.

#### 4. TUBERCULOUS ADENITIS

##### (a) *Bronchial*

Tuberculous disease of the bronchial glands is one of the most striking features of tuberculosis in infancy and early childhood. These glands are conveniently grouped as: (1) Peritracheal—surrounding the trachea; (2) Tracheo-bronchial—at the bifurcation and around the primary bronchi; (3) Pulmonary—which follow the course of the bronchi as far as the fourth division.

These groups of glands are connected with one another by lymphatic channels, and hence disease in one group tends to spread to the others. All groups are usually involved at the same time, but in varying degrees. The affected nodes vary greatly in number and size. Frequently the more deeply situated glands are the most involved, and from them an extension of the process often takes place. The usual tuberculous process results. Suppuration is not infrequent, while calcification is rare. Although the process has gone on to caseation the mass may become encapsulated and remain thus for years. At any time, however, the old process may be lighted up. Secondary lesions may occur. There may be pressure upon, or irritation of, the vagus and recurrent laryngeal nerves. There may be compression or ulceration of the oesophagus, trachea, bronchi, or superior vena cava. If suppuration occurs there may result a true mediastinal abscess which tends to point in the first or second right interspace close to the sternum or in the suprasternal notch.

##### (b) *Cervical*

In Treves' series of 155 cases of scrofula, 90% occurred in the cervical glands. Tuberculosis in other external glands was rare without coincident infection of the cervicals. It is usually the result of a descending infection from the rhinopharynx. Frequently the portal of entry is the tonsillar and adenoid tissue. It is more often found between the ages of three and ten years, and is usually unilateral. It may be acute or chronic.

(1) *Acute form.*—Here the process is rapid and tends to early caseation and softening. The products of inflammation are mainly cellular, and there is little fibrous tissue. Inflammation within the gland is followed by involvement of the surrounding tissues, resulting in adhesions or the formation of a peri-glandular abscess. The caseous mass may become encapsulated, or softening may occur at one or more foci and an abscess form. As the abscess formation progresses the process gradually extends towards the surface, involving the cellular structures, and finally the skin. Such abscesses frequently become secondarily infected. The usual tendency, however, is for the process to subside into the chronic form.

(2) *Chronic form.*—This includes the greater number of cases. The

process is more insidious, fibrous tissue predominates, and caseation and softening occur late or not at all. The nodes are not as vascular as in the acute form. They are tough and hard, and appear like small fibrous tumours. There may at first be only one node affected but the process soon spreads to involve the other glands. Throughout the course there is apt to be one node definitely larger than any others. As the enlargement progresses a mild peri-adenitis occurs, which tends to obscure the outline of the glands, and forms them into a solid mass binding them more or less firmly to the adjacent tissues. In most cases there is a tendency for the inflammation to subside spontaneously about the time of puberty. Calcification is rare.

(c) *Mesenteric*

Tuberculosis of these glands always occurs in the course of tuberculous enteritis and may be found independently. Rarely, depending on size and position, the diseased glands may exert pressure on the inferior vena cava, producing oedema of the legs or thrombosis of the vein, or pressure on the portal vein, causing ascites.

## 5. TUBERCULOUS ENTERITIS

Intestinal infection is usually secondary to disease of the lungs, presumably from sputum which is swallowed. Thus it is more frequent in older children than in infants. The lesions are most often found in the lower ileum, although they may occur anywhere. The jejunum is frequently also involved and in extensive disease the process may spread to the large intestine, chiefly the caecum. The appendix may also be involved. Tuberculous enteritis consists in ulceration which starts in Peyer's patches, as tiny yellow nodules, which soon break down to form ulcers. The lesions vary greatly in number and size. The ulcer is irregular in shape, excavated, with rounded overhanging borders and a deep red infiltrated edge. The surface is covered with granulations. The longest diameter of the ulcerated area is at right angles to the intestinal axis. Healing is followed by cicatrization which, however, in such favourable cases, is rarely great enough to produce stricture of the gut.

## 6. TUBERCULOUS PERITONITIS

It is possible for the peritoneum to be involved as the primary lesion of tuberculosis, but usually the condition is secondary to disease of the intestines, mesenteric glands or other parts. The bovine type of bacillus is more frequently found in this than in any other form of tuberculosis. It is usually a subacute or chronic condition. It may be fibrous or ascitic.

(a) *In the fibrous form* there is production of a large amount of fibrous tissue in which there are large caseous deposits. Thus there are formed extensive adhesions within the abdomen. In some cases there may be fluid which is often sacculated. Tuberculous deposits upon the intestinal wall may lead to perforation. The abdominal wall may be involved resulting in abscesses, which may open externally.

(b) *The ascitic form* is much less common. The peritoneum is thickly studded with miliary tubercles. There is production of a moderate amount of fibrin and a great deal of straw-coloured serum. In very chronic cases the serum may be sacculated.

## 7. TUBERCULOSIS OF BONES AND JOINTS

Tuberculous disease of bone occurs most frequently in the vertebrae and about the hip and knee joint. It usually begins from the third to the eighth year. In infants the bones of the hand are often involved. The condition usually occurs as a primary lesion, but is always secondary to a tuberculous focus elsewhere, often in the bronchial glands. It begins as an osteitis, which in long bones is present at the extremity, in short bones in the centre. Caseation and even breaking down of the bone may follow. In the case of the long bones the joint is often involved. Cure consists in the separation of the broken down material and formation of healthy bone. The involved joint becomes ankylosed, usually in an abnormal position. Disease of the bones of the hand, or tuberculous dactylitis, involves the short, tubular bones. The swelling causes expansion of the bone and thinning of the shaft until a mere shell remains. Involvement of the periosteum and soft tissue is followed by abscess and sinus formation, and the exfoliation of sequestra. Healing results in marked deformity. The average duration of tuberculosis of bone is three years. Amyloid degeneration of the liver, spleen and kidneys often occurs at the same time.

8. Tuberculosis may involve any organ. The structures most commonly affected, apart from those already described, are: skin, spleen, liver, heart, stomach and genito-urinary organs. Phlyctenular conjunctivitis, found mostly in children, is usually considered to be tuberculous.

## CLINICAL FORMS OF TUBERCULOSIS

### 1. GENERAL TUBERCULOSIS

Many children who are infected harbour somewhere in their body for a variable length of time a pathologically active tuberculous focus which may be unsuspected. There may be vague constitutional symptoms due to the toxæmia. These show great variation and no pathognomonic features, and may constitute many ill-defined conditions of ill-health in infancy and childhood. The general symptoms often precede the local ones, but are seldom recognized until the process is quite well advanced in some one organ. Tuberculous disease should be suspected in a child whose vitality remains persistently lowered, especially when certain other indications are present.

#### (a) *Signs and Symptoms*

(1) In infancy.—Failure to gain in weight is often the earliest symptom. The infant is pale and does not thrive no matter how fed. There may be fretfulness and disturbed sleep.

(2) In older children.—There is often an unusual disposition to lie around, peevishness, with loss of appetite, and failure to gain in weight. They are undernourished and possess poor tissue turgour. There is a moderate secondary anaemia. After a few weeks fever develops. A persistent rise up to 99° F. with a subnormal temperature in the morning is characteristic. A rise in temperature after exercise, which persists for one hour while the child is completely at rest, is suspicious.

(b) *Diagnosis*

In general, as well as in all other forms of tuberculosis, the following must be considered.

(1) History.—(i) Family History—It should be carefully noted whether there is any predisposed susceptibility as denoted by any suggestive disease in parents or grandparents. (ii) History of Exposure—In the majority of cases of tuberculosis in childhood a history of exposure to an “open” case can be developed. When this is not possible those who come into most intimate contact with the child should be examined. Inquiry should be made as to whether members of the household, frequent visitors, or those whom the child visits, are subject to a “chronic cough.” (iii) Past History—A history of certain diseases may be veritable sign posts for diagnosis, *e.g.*, a protracted convalescence from measles or whooping-cough, forming a continuous link to the present disease, or repeated and protracted attacks of broncho-pneumonia in older children. A history of a chronic cough with persistent coryza producing a chronic dermatitis of the alae nasae, an idiopathic or primary pleurisy, dry or with effusion, a painless otitis media not improving under treatment, a chronic cervical adenitis lasting several months and occurring after two years of age, are all suggestive of tuberculous disease. (iv) Environment—overcrowding, poverty, filth, lack of fresh air and sunshine, all must be considered.

(2) Physical Examination.—An appearance of ruddy health does not exclude tuberculosis. In its incipency the disease does not produce any recognizable mark upon the child's physical appearance. Only in the prolonged or severe cases do we see the characteristic appearance of phthisis in the adult. Physical examination may reveal the signs already mentioned, together with a dry, inelastic skin, and possibly some healed lesions of skin tuberculosis, or old scars, or fistulae of tuberculous adenitis.

(3) Tuberculin Tests.—For diagnostic use in children either one of two methods of applying the test may be used.

(i) The intracutaneous method.—This is the most delicate test. The skin of the anterior surface of the forearm is washed with alcohol and allowed to dry. Then .01 mgm. of O.T. tuberculin is dissolved in .1 c.c. of saline solution and injected intracutaneously, so that a pale elevated area is produced. A control test with simple saline solution is made at the same time. A positive reaction consists in a reddish discolouration at the point of injection and an induration which can be readily felt. This usually appears in 24 hours and remains for several days. The test should be read at the end of 48 hours.

(ii) The von Pirquet method.—The best site for inoculation is the outer side of the forearm. A small drop of pure tuberculin is placed upon the skin, which has been previously washed with alcohol and allowed to dry. After making a control scratch with a sterile needle, fully two inches from the tuberculin, a similar scratch is made through the drop, each scratch being less than one-quarter inch long. If excessive reaction occurs it is best to cover the arm with gauze to prevent infection. The reaction consists in a red areola and a slight induration and occurs in several forms.

(1) The usual reaction appears in 12-18 hours, reaches its maximum

intensity in 24 hours, remains at its height for one to two days, and then gradually disappears in three or four days, being followed by a slight local desquamation.

(2) A rapid reaction which may occur in 5-6 hours and disappears in 10-12 hours. It may be readily overlooked and is not of diagnostic importance.

(3) An intense reaction which appears about the same time as the first form, but may take two or more days to reach its maximum. Rarely vesiculation may occur.

Dr. Alan Brown maintains that in order to obtain uniform results, the latter method should be used exclusively, it being the simplest, and therefore the most satisfactory. It is advisable to make a cutaneous test in every infant suffering from a respiratory disease, or in case of obscurity where tuberculosis is suspected. In a child in whom tuberculosis is suspected the test should be repeated if the first proves negative. In infancy a negative cutaneous reaction, except in moribund cases or in children suffering from measles, is almost conclusive evidence against the existence of a tuberculous focus. It is believed that if the tuberculin test is negative, in a child who was exposed four months previously, the child was not infected by that exposure.

(4) X-Ray Examination.—This, if properly interpreted, forms one of the most valuable methods of diagnosis.

## 2. PULMONARY TUBERCULOSIS

If the early tuberculosis goes on to the development of the frank form the lungs are usually involved. In infants there develops a slight cough which is rarely severe. There is a moderate fever of 101-102° F. In older children, often after a period in which the symptoms subside somewhat, the condition may become rapidly worse. An irregular fever develops and is followed by wasting. Occasionally in infancy, and often in childhood, the process manifests itself as an acute pneumonia.

### (a) *Tuberculous Bronchopneumonia*

This condition may be preceded by constitutional symptoms, as previously described, or it may follow an attack of supposedly simple acute bronchitis or bronchopneumonia, which is primary or secondary to measles, whooping-cough or influenza. The onset is usually insidious and the progress gradual.

Holt considers tuberculous bronchitis as a separate entity, but in most cases this is simply the earliest clinical stage of tuberculous bronchopneumonia. Cough—at first is very slight, later is more severe and may be paroxysmal, resembling pertussis. It may be hard, dry or suppressed. Expectoration is rare in children under five years of age. The material brought up is swallowed. Respirations are much increased, out of proportion to the temperature. Fever at first usually 100-102° F., later is usually higher but does not bear much relation to the extent of the disease. Progressive weakness and anaemia are associated with wasting. Pulse is rapid in the early stage and continues so throughout. These symptoms become gradually worse until the child dies in one to three months. The end is marked by cyanosis, great dyspnoea, weak pulse, and extreme prostration. An occasional case dies from meningitis, while, on the other hand, the condition may pass into a chronic fibroid pneumonia.

In the lung the physical signs are those of a simple bronchopneumonia or sometimes they may be almost absent. There are areas of consolidation as shown by dullness, bronchial breathing, bronchophony and medium rhonchi. These signs may be scattered throughout both lungs, or localized in the upper lobes. The patient may die before signs of complete consolidation are present.

Tuberculous bronchopneumonia differs from the simple type, in having a more gradual onset and slower course. The general symptoms are out of all proportion to the physical signs.

The diagnosis is, of course, clinched if the bacilli can be demonstrated. This is not as difficult as has been supposed. As there is no expectoration, the sputum should be obtained by exciting a cough by irritating the pharynx, and then catching the sputum upon a small swab. Often repeated examinations are necessary. It is sometimes easier to find the bacilli in the stools than in the sputum. Their presence here is far more likely to indicate pulmonary tuberculosis than involvement of the intestines. The organism, however, must be carefully differentiated from the smegma bacillus.

#### *(b) Miliary Tuberculosis*

This condition is not very common but may be found even in young infants. The diagnosis is very frequently not made until autopsy, since the symptoms and physical signs are obscure and indefinite.

Signs and symptoms are often very few or very indefinite. The most characteristic feature is a slight fever, usually about 101° F., which cannot be accounted for. Respirations are only slightly increased. There is no rapid wasting. Later the whole condition becomes more exaggerated, attacks of cyanosis occur, and the child dies in two to six weeks from the onset of symptoms. As a rule the pulmonary signs predominate but cerebral signs may occasionally develop.

In the lungs there may be only a few scattered, fine, moist rales, which are variable. The liver and spleen are usually enlarged in the later stages.

In infants, because of the loss of weight and asthenia, the condition must be differentiated from marasmus. In older children typhoid fever must be ruled out. In the more severe forms differentiation may be impossible.

#### *(c) Chronic Phthisis*

This form of tuberculosis is rarely seen up to the twelfth year, when it resembles the same disease in adults. As mentioned before, a chronic tuberculous bronchopneumonia, somewhat resembling this condition, occasionally is found. This follows some acute form from which there is only partial recovery. The child does not regain his former weight or vigour. From time to time more or less severe exacerbations occur, which pass under the names of bronchitis, bronchopneumonia or pleurisy.

#### *Treatment*

Treatment of all forms of pulmonary tuberculosis is symptomatic and constitutional. Pneumothorax may be employed in selected cases. The indications and technique are the same as in adults.

### 3. TUBERCULOUS PLEURISY

This only occurs when there is a tuberculous lesion elsewhere in the chest, and since the symptoms, diagnosis and local treatment of tuberculous pleurisy do not differ from the more common forms in infancy and childhood they will not be described here.

### 4. TUBERCULOUS MENINGITIS

Tuberculous meningitis is produced by the transportation of the bacilli to the brain in the blood stream. In infants and young children, although it rarely happens that pulmonary lesions are absent, the signs of meningeal disease often occur before there are clinical manifestations elsewhere. In older children there may have been previous evidence of tuberculosis in the lungs, bones or lymph glands.

#### (a) *Signs and Symptoms*

(1) The prodromal symptoms have a gradual onset and may be very indefinite and variable. They consist of listlessness, asthenia, and change of disposition, loss of appetite, vomiting, with no relation to meals and which disappears in a few days, constipation, fever, which develops towards the end of this stage, is slight but continuous.

(2) The cerebral symptoms develop in from a few days to 2-3 weeks from the onset. Usually the first pronounced symptom is persistent increasing drowsiness. Irritative stage consists of: Headache in the frontal region. Photophobia occasionally. Pain indicated by sudden screaming-out at night. Wasting chiefly in limbs and abdomen. Fine tremor of the hands. Pulse accelerated. Expiration is prolonged.

Depressive stage consists of: Drowsiness passing into stupor from which child can be roused. Finally coma develops. Pulse slow and irregular. Respiration is frequently Cheyne-Stokes in character. Fever—slight, 100-101° F.

In infants death usually occurs in 2-3 weeks from onset of symptoms. In older children the progress of the disease is slower and subject to remissions. In them death may not occur for 6 weeks.

#### (b) *Physical Examination*

(1) Irritative Stage.—Stiffness of the neck appears with the drowsiness. This is elicited by grasping the head in both hands and gently flexing, extending and rotating it. Skin is slightly hyperaesthetic. Pupils are normal or contracted, often unequal, react sluggishly and nystagmus may be present. The patellar reflex may be normal, exaggerated or diminished. Kernig's sign is often absent in babies. Brudjinski's sign can often be elicited.

(2) Depressive Stage.—Opisthotonus usually present. Skin, the *tâché cérébrale* appears as a bright red flush along the line of stroke of the finger-nail, or as a white line which changes to red and persists for several minutes. Pupils are unequal and do not respond. Transient Paralysis—Strabismus, ptosis of one eyelid, facial paralysis, monoplegia or hemiplegia may be present. There may be frequent automatic movements of the hands or muscular twitchings. In infants the fontanelle is tense and bulging.

*(c) Diagnosis*

Careful examination may reveal the presence of tubercles in the choroid coat of the eye. Early, the leucocyte count is normal, later it rises to about 30,000, of which about 80% are polymorphs. A positive diagnosis is made only by lumbar puncture. The fluid is usually perfectly clear and the usual cell count is from 100-150 per cu. mm., with 95% lymphocytes. After standing for twelve hours in an incubator a central fibrin coagulum forms, in which the bacilli are usually entangled.

Death occurs in 100% of cases.

Treatment is useless, but is carried out for the sake of the relatives. The child should be made as comfortable as possible. Daily withdrawal of C.S.F. in quantities of 5 c.c. may be helpful. Feeding of albumin-milk is advised by some and may be given by nasal catheter.

*(To be continued)*

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## EPIDEMIOLOGY OF POLIOMYELITIS\*

A. M. JEFFREY, M.B.

*Brief History*

Epidemiology studies disease in the community much as clinical medicine studies it in the individual. Just as clinical medicine borrows freely from laboratory investigation, so also does epidemiology make use of experimental medicine and bacteriology in interpreting field work.

As much progress of this study dates from the application of bacteriology, and as epidemiological studies as we know them now do not go back so very far, our history of epidemics of this disease may be very incomplete.

It must be remembered, however, that present day conditions are different from those of the past, and that the civilized world not only contains more people but that people travel more freely. These new conditions should favour the spread of such a disease as poliomyelitis. Therefore large epidemics of this disease may be a new feature. It may not be simply a lack of records.

It was interesting to stumble across the information in Sir Walter Scott's biography that he was born in 1771, and that at the age of 18 months he had a teething illness resulting in lifelong lameness. At any rate, whether or not this may have been poliomyelitis, it was not until the last century, and particularly in the latter half of it, that we find the first records of small epidemics of poliomyelitis, and so far as we know the first recognition of the disease as a clinical entity.

In the first two decades of the present century epidemics increased in number and in size, each one tending to surpass the previous one in the number of its victims. What has occurred in the incidence of this disease might be described as an epidemic of epidemics.

*Manner of Spread*

Careful studies of some epidemics show that the disease tends to spread radially from foci, and while in one community it may have reached its crest and be subsiding, in the adjoining territory the number of cases are on the increase, and so on. This regular spread is by no means the rule. Very often the disease jumps over intervening populated area in such a way as to suggest place infection.

On the other hand, the spread is generally along the lines of human travel, and the rapidity of spread points to man as the carrier. This irregular spread of the disease in its disconnected way, with apparent lack of contact between cases, suggests the vehicle of abortive cases and healthy carriers as the means of conveyance. In support of this the nasal passages of healthy people exposed to the disease have been shown to harbour the virus.

Cerebrospinal meningitis is a disease generally believed to be spread directly from person to person through the agency of human carriers. This disease and poliomyelitis have much in common

- (1) in their age incidence.
- (2) in their having a low attack rate, seldom having more than one case per family.
- (3) in their rapid spread over large areas, showing a tendency to skip over localities, apparently without cause.

Studies of cerebrospinal meningitis have been easier because of the demonstration of the causal agent by bacteriological means. The carriers can be identified. In the two diseases having so much in common what is accepted for the manner of spread of one might at least be reasonably inferred for the other; that is, that the abortive cases and healthy carrier are the important means of spread of both diseases.

*Seasonal Incidence*

The seasonal incidence has given rise to much discussion. For it is claimed that if poliomyelitis is spread by nasal secretions and by human contact, then it is strange that it should have a gastro-intestinal seasonal incidence instead of a winter one. This has stimulated entomological investigation. Poliomyelitis is not always confined to this summer incidence. There have been exceptions. Groups of cases have been reported occurring in the winter months.

*Factors Limiting the Spread of Poliomyelitis.*

- (1) Variation in the virus itself.
- (2) In the acquired immunity of contacts.
- (3) In the local defences of the individual against infection.

(1) Flexner and Amoss have recorded changes in activity in virus preserved for a long time with periodic passage through experimental animals. The human virus at first was greatly enhanced by passage through monkeys, but after a time dropped back again to its original virulence. After preservation for a long time, however, the virus had

again taken on an increased activity, apparently without any ascribable reason. Possibly in nature the virus varies in a similar manner.

(2) That acquired immunity helps to check the spread of the disease is suggested by

- I. Experimental work, in which a series of healthy contacts were examined for immune bodies in their blood. These were shown to be present in over 60% of those examined.
- II. The age incidence of infancy and early childhood is suggestive as the age most likely to lack acquired immunity.
- III. In the rural districts not only is the rate of attack higher in contacts, but more adults have the disease.
- IV. In any community an epidemic is seldom followed by another without an intervening lapse of at least a few years. The epidemic seems to depend on the presence of susceptible children.

These facts point to acquired immunity as a factor controlling the epidemicity of the disease.

(3) Local defences against infection of the central nervous system.

The attack rate (typical cases) in cerebrospinal meningitis, encephalitis, lethargica, and poliomyelitis is low. It seems that an upper respiratory infection, given a reasonable opportunity, has little difficulty in producing others. The same is true for a gastro-intestinal disease, such as typhoid. But it does appear much more difficult for an infection of a central nervous system to reach and infect another central nervous system.

It is noteworthy in experimental work that, aside from the intra cerebral route, other modes of infection give more or less inconstant results, and that the external portal most favourable to the attack of the virus is the nasal mucous membrane. In this connection it has been shown that concentrated nasal washings of healthy people have shown neutralizing powers over the virus.

While the intravenous route is unreliable, it has been made effective by first injecting intraspinally horse serum, presumably damaging the choroidal plexus. Infection by the nasal route in the presence of a damaged choroidal plexus may be checked by administering immune serum intravenously. While in the non-immunized controls infection occurred.

From the above data it may be inferred that the local defences comprising at least the nasal secretions and the choroidal plexus may be instrumental in cutting down the attack rate.

### *Summary*

Epidemics of poliomyelitis have increased in number and in size in recent years.

Its manner of spread is similar to other acute infections of the central nervous system, and the human carrier is considered to be the chief means of spread.

The limit of spread may be influenced by variations of the virus, by acquired immunity, and by the natural local defences possessed by anyone against infection of the central nervous system.

\*The first of a series of three papers on Anterior Poliomyelitis delivered before the Academy of Medicine on November 26th, 1925. This insidious disease is of particular interest on account of last summers mild epidemic in Toronto, during which some forty cases were treated in the Hospital for Sick Children alone. The remaining papers will appear in subsequent issues.

## ABNORMALITIES IN BLOOD PRESSURE

T. ALLEN SWEET, '26

Alteration in blood pressure from the normal in the direction of hypo- or hypertension is a frequent sign in many pathological conditions. A few of these will be briefly mentioned.

I. *Acute or Transient Hypotension*.—This is encountered in large sudden hemorrhages, the factors in its production being (1) depression and later paralysis of the vasoconstrictor centre; (2) of minor importance, decrease in total blood volume; (3) decreased peripheral resistance, inasmuch as a large amount of blood is diverted from the capillary bed. In surgical and traumatic shock it would seem to be due chiefly to an accumulation of blood in the smaller venules and capillaries, with a consequent lessened flow to the right auricle. This accumulation may be due to direct injury of the part or vascular poisons absorbed from the injured tissues.

II. *Chronic Hypotension*.—Is often observed in various wasting and febrile diseases; among the former, chronic diarrhoeas, among the latter, typhoid fever and active tuberculosis. It is sometimes present in Addison's disease, when it is considered due to lessened adrenal secretion.

IIA. Under chronic hypotension we meet with a group of cases where the low blood pressure is the chief objective finding—so-called "*Essential Hypotension*." There has as yet been no adequate explanation of its cause. It has been attributed by various authors to endocrine disturbances, chronic infections, enteroptosis and psychic causes.

III. *Acute or Transient Hypertension*.—This occurs in acute asphyxia, due to retention of CO<sub>2</sub>, increase in hydrogen ion concentration, and consequent stimulation of the vasoconstrictor centre. In acute cerebral compression, due to anaemia of the vasomotor centre, with a local lack of oxygen and local accumulation of CO<sub>2</sub> and other acids.

IV. *Chronic hypertension*.—In our present state of knowledge we can define under this four main groups: (1) Hypertension accompanying Bright's disease; (2) hypertension associated with arterio-sclerosis; (3) hypertension with arterio-sclerosis and cardia-renal disease; and (4) essential hypertension. On account of the immensity of the subject it has been deemed necessary to limit the remainder of this paper to a consideration of the last group.

*Essential hypertension* is a "malady in or at middle life in which there is an excessive rise in blood pressure without any cardiac hyper-

trophy and altered blood vessels, the raised blood pressure being the only sign of the disease."

That, though so commonly associated, arterio-sclerosis cannot be the cause of the hypertension has been proved by the vast amount of clinical and pathological evidence brought to bear upon the problem. Nor is it logical; for the hypertension which varies so quickly and markedly and so frequently in these cases could not be due merely to an occlusion of the arteries by internal disease since such internal changes could not undergo such a quick parallel alteration. It is now generally conceded that hypertension exists primarily while arterio-sclerosis and cardio-renal disease, if they do occur, are consequent to it, or the same cause acting over a longer interval or a combination of the two. The time elapsing before the onset of the arterio-sclerosis varies widely, but in some cases it is said to be obvious within a year. This change in the vessel may be a simple hypertrophy of the musculo-elastic coat of the intima and of the media, without inflammatory change in adaptation to strain, or the result of a deleterious substance present or both. That this vascular change may involve the small vessels rather than the larger (temporal, brachial or radial) is suggested by some case analyses of O'Hare and Walker. They procured two groups of cases I. non-hypertensive cases with peripheral sclerosis II. hypertensive cases with large artery sclerosis. As an index of small vessel arterio-sclerosis they examined the retinal arteries ophthalmoscopically. In cases of group one they found little or no retinal arterio-sclerosis—in those of group two, marked. The degree of sclerosis bore no quantitative relation to the degree of hypertension, but they noted a greater tendency to arterio-sclerosis of the retinal artery where the diastolic pressure was high. In addition they came upon four cases with normal blood pressure, large artery sclerosis and marked retinal arterio-sclerosis. In both of these there was found to be a previous history of hypertension. Cohen also points out that even by the most careful ophthalmoscopic examination some retinal vessels appearing perfectly normal, microscopically show definite arterio-sclerosis. In other cases where the retinal arteries are only slightly sclerosed the choroidal are often markedly so.

Theories advanced as to the cause of essential hypertension are legion. Many have passed but many have remained, and each has its little band of faithful followers scattered throughout the scientific world. It will probably, therefore, not come amiss if some of the more important of these are mentioned.

I. Heredity has been claimed, inasmuch as cerebral haemorrhage appears to be, and these two conditions commonly accompany one another.

II. Various glands of the endocrine chain have been suggested by different authors. It has been noted that hypertension often accompanies marked obesity and some cases of this are regarded as being of endocrine origin. Sargent and Cottintot reduced the blood pressure in 12 cases of hypertension by radiation of the adrenals. Hirsch obtained hypertension followed by arterio-sclerosis in rabbits by repeated injections of adrenalin intravenously. Sajoris claims hypertension is brought about by disturbances of the endocrine triad, adrenals, thyroid and pancreas in the direction of toxic product formation, due to the inadequate catabolism of both tissue and food wastes.

III. It has often been connected with high sodium chloride consumption. The Hindus are said to have a universally low blood pressure, and are meagre salt users. Mosenthal and Short found no ill effects using high salt diets on cases of essential hypertension, and O'Hare and Walker point out that it is illogical to believe that sodium chloride metabolism changes could occur so rapidly as to produce the sudden and often marked changes in blood pressure seen in these subjects.

IV. Some authors place the onus upon high protein diets. O'Hare and Walker found no aggravation of the condition in hypertensive cases fed on high protein diets. Munk and Newburgh obtained hypertension and arterio-sclerosis in guinea-pigs on a high protein intake. Benedict on low protein and low caloric diets reduced the normal blood pressure in a large number of presumably normal young adults.

V. It is not to be wondered at that intestinal intoxication should come in for its share of the blame. Certain products are said to be formed by the action of putrefactive organisms on proteins in intestinal stasis. Amylamine has been suggested, while Metchnikoff puts forth claims as to the toxicity of Indol. Hypertension seems to have no higher incidence in those suffering from chronic intestinal stasis than in those who do not.

VI. Popielski upheld the cholin salts, but no observer since has been able to demonstrate that cholin or its salts are capable of raising blood pressure.

VII. Psychic or neurotic cause. Essential hypertension has often been noted, particularly in neurotic subjects and those who undergo persistent mental and physical strain. This conception has been gaining ground of late years.

VIII. Goepp identifies certain cases with focal infections. Barach, in a study of 68 cases of essential hypertension, inclines to his view.

Major and Stephenson, at Johns Hopkins, discovered that they could elevate the blood pressure of dogs (even doubled or trebled) within a few minutes by the intravenous or intramuscular injection of 0.1-0.2 gms. of Methyl-guanidine sulphate per kgm. body weight. This elevation was sustained for four to five hours. Section of the vagi did not alter the results, and any of the guanidine compounds had the same action. The same elevation was also obtained in decerebrate dogs showing that the rise is in part at least due to peripheral vasomotor action. A 10% solution of calcium, potassium or ammonium chlorides in doses of 0.1 gm. per kgm. body weight produced a prompt and persistent fall of blood pressure to normal. Methyl and dimethyl guanidine are present in normal urine. The excretion of guanidine bases in essential hypertension cases they found to be lessened. A chronic nephritic with normal blood pressure showed a high guanidine output. The kidney seems to be very finely balanced to the excretion of these substances. Jaffe maintains in cases of universal arterio-sclerosis that that in the kidney is usually most marked. Sclerosis of the blood vessels of the pancreas is sometimes almost as marked, but the kidney is the only organ in which well-characterized destruction of the parenchyma follows. Arterio-sclerosis of the spleen is so constant after 40-50 years of age as to be considered physiological. Löhlein described marked dilatation of the arterioles of the kidney preceding sclerosis and was confirmed by

Fahr. Jaffe examined post mortem the kidneys in essential hypertensive cases, and found sclerosis of the capillary tufts indicating a direct injury to the glomeruli. It is conceivable that this first injury leads to contraction of the capillary tufts without destruction of their walls. If the injury is continuous, and the spasm frequently repeated, visible changes finally result in the capillaries. By this contraction of the tufts the blood flow through the glomeruli will be interrupted, and the irritating agent held back will accumulate in the arterioles, bringing about an effort of contraction, and this against increased resistance. As the muscle coats of the vasa afferentia are too insignificant to compensate successfully for this increase in work, other parts of the circulation will react to keep up the renal circulation, and at the point of resistance the thin walls of the afferent vessels will be distended. He (Jaffe) considers that sudden and repeated elimination of an important part of the circulation in this way will increase the heart action and raise the blood pressure.

Monakou, Pol and others have emphasized the spasm of small arteries in explaining essential hypertension. Some claim the spasm first affects the arterioles, others the capillaries. In the kidney the dilatation of the arterioles in early hypertension suggests rather spasm of the capillaries of the tufts. The arterio-capillary spasms may not be confined to the kidney, for they may occur in other parts of the body, but disturbances mainly in the renal blood flow may play an important role in altering blood pressure. Jaffe believes that, as a result of this direct toxic injury to the arteries in the later stages, we get proliferation of the intima, hyaline and lipoid degeneration; and that the extent of the degenerative changes can be explained by the different quality and intensity of the injurious agent. Whether these recent inquiries have more nearly approached the truth we cannot with certainty state. It seems that we must almost wholly indulge in generalities as yet.

After such a survey of the subject we can, however, conclude that the origin of essential hypertension is psychic, or due to a substance or substances present in the body, either an increased normal metabolite or an aberrant metabolite bringing about spasm of the capillaries which may or may not be followed by arterio-sclerosis or cardio-renal disease. This substance may act centrally or directly on the vessel wall, and the arterio-sclerosis resulting due to hypertension per se or the direct deleterious action of the substance circulating in the blood.

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## FACULTY NOTES

### Medical At-Home

The Annual Medical At-Home was held in the Crystal Ball Room of the King Edward Hotel on Tuesday, February 2nd, and again proved itself the social event of the University year. Supper was served in the Pickwick Room, where the many novelties, streamers and paper caps added to a very colourful picture. The patronesses were: Mrs. A. Primrose, Mrs. J. J. R. Macleod, Mrs. C. L. Starr, Mrs. W. B. Hendry, Mrs. J. Oille, Mrs. S. Ryerson and Mrs. R. Janes. Visiting guests were present from McGill, Queen's, Western and O.A.C., as well as repre-

sentatives from our sister faculties of Arts, Applied Science and Dentistry. The music was supplied by Romanelli's orchestra, and the dances were interspersed with many novelties which greatly enhanced the enjoyment of the evening.

The committee in charge deserve great credit for the efficient manner in which preparations for the dance were carried out. It was comprised of the following members: W. L. Deeton, J. B. Laidlaw, O. A. Kilpatrick, W. A. McTavish, N. L. Murray and B. B. Sparks.

### **Academy of Medicine**

The graduating year were the guests of the Academy of Medicine at a special meeting on Friday, February 5th. The privileges of the Academy were graciously extended to the members of the year. The aims and activities of the organization were made clear and a number of very interesting subjects considered. Refreshments served to complete a very enjoyable and profitable evening.

### **Daffydil Committee**

Reports from the Daffydil Committee give promise of a highly successful entertainment, well in keeping with the best of its traditions. The dates are the 11th and 12th of February, with the annual Daffydil Banquet on the following evening. Each year skit is preparing a stunt, incorporating the better parts of their Daffydil performance for this occasion. Representatives of sister institutions have been invited.

### **Interneship**

During the latter weeks of the past year and the first part of January questionnaires were sent from the Secretary's office to the members of the last two graduating classes in an endeavour to gather information about interneships in various hospitals in which these graduates have served. These forms are comprehensive and contain much valuable information, and in many instances the opinion of the interne or recent interne with respect to the advantages and disadvantages peculiar to the hospital at which he served. Many replies have been received and can be seen at the Secretary's office.

### **Medical Sick Benefit Fund**

The Medical Sick Benefit Committee report that 463 tickets have been sold this year as compared with 480 during the 1924-25 session, in which there was a slightly greater registration. Neither figure fulfils the expectations raised by the support afforded this institution on its foundation the preceding year.

### **Medical Society**

Mr. Justice W. R. Riddell addressed a capacity audience at an open meeting of the Medical Society in the Medical Building on Friday, January 22nd, at 5 p.m. Choosing as his topic "The Doctor in Court,"

he briefly and fascinatingly outlined the various situations in which medical men appear in court and gave much invaluable advice as to their conduct in such cases.

A very poorly attended open meeting of the Medical Society, of a purely business character, was held in the Medical Building at 5 p.m. on Friday, January 29th. A proposed amendment to the constitution, designed to prevent the possibility of having more than three candidates for any one Medical Society office by preliminary year elections, was unable to obtain the necessary majority by two votes. The Medical Society elections were announced for February 19th. The faculty have declined to declare a half-holiday for this occasion. It was suggested, but not definitely decided, that the Medical Banquet should be held on the evening of this day. President Biehn remarked that the activities of the Society had been considerably cut down by their inability to obtain a Reading Room and the existence of a large number of sixth year Reading Clubs sponsored by the staff. He added that it was partially to offset this disability that the JOURNAL had been established. It was pointed out that the duties of the sixth year president included those of chairman of the Medical At-Home Committee.

Mr. H. E. Rykert represented the Medical Society at the Annual Arts Ball held in Hart House on Friday, January 29th.

Mr. O. A. Kilpatrick represented the Medical Society at the Annual At-Home of the Ontario Agricultural College, Guelph, on February 5th.

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### The University of Toronto Medical Journal

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## Athletic Society

The Medical Water Polo Team have now brought the third inter-faculty championship of the year to us. The playing of Flommerfelt, Moir and Derbyshire is to be highly commended. 2T8 has especial cause for congratulation over this victory as she has been represented by six players on this team in addition to Manager Hetherington.

Without being greedy, we hope that our Boxing, Wrestling and Fencing teams, and possibly one of our four Basketball and Hockey teams may also bring home a championship. May we really make this a year hard to equal again—a goal for future attainment!

At the Medical Banquet in February, on Election Day in Medicine, athletics will play a prominent part, and those who have served Medicine so well in sport this year will be honoured. Turn out and applaud them.

**President of U. of T. Rugby Club**

For his election to the office of President of the University of Toronto Rugby Club, 2T8 is unanimous in its congratulations to MacMasters, and expresses the sincere wish that he will head an organization that will bring a longed-for cup to the U. of T. next fall.

## The University of Toronto Medical Journal

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